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Behavioral and neural correlates of congenital amusia

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Résumé

Les objectifs principaux de cette thèse étaient de mieux comprendre le développement anormal et normal du traitement musical dans le cerveau. Pour ce faire, nous avons effectué quatre études sur les corrélats comportementaux et cérébraux de l'amusie congénitale, une trouble spécifique lié à la musique qui empêche des individus normaux, d'aquérir des compétences musicales fondamentales. Les données de la littérature indiquent que l'amusie congénitale serait liée à un problème perceptif de bas niveau concernant la discrimination des hauteurs. Dans la première étude, notre objectif était de mieux détailler ce trouble et d'évaluer sa spécificité en comparant un groupe de sujets amusiques adultes à des sujets contrôles n'ayant pas de troubles musicaux. Pour ce faire, les sujets écoutaient des séquences de cinq tons tous de même hauteur dans un rythme régulier, sauf pour le quatrième ton qui était modifié soit en terme de hauteur, soit en terme de rythme. Les sujets avaient pour tâche de détecter un éventuel changement. Comme prévu, tous les sujets amusiques ont eu des difficultés à discriminer les changements de hauteurs, mais pas les changements temporels. Ces résultats confirment que les amusiques ont un trouble sévère et spécifique de la discrimination fine hauteurs. Ce trouble pourrait s'expliquer par une anomalie cérébrale. Afin de vérifier cela, une deuxième étude en imagerie par résonance magnétique (IRMf) a été conduite chez des sujets universitaires sans troubles musicaux, pour identifier les mécanismes cérébraux impliqués dans la perception de hauteurs. En accord avec de précédents résultats, le cortex auditif droit décode plus finement les changements de hauteur que le gauche. Dans une troisième étude en IRMf, un paradigme similaire a été utilisé afin d'explorer les structures cérébrales impliquées dans la discrimination des hauteurs et temporelle, chez des sujets amusiques et des contrôles appariés, sans problèmes musicaux. A l'encontre de nos prédictions, les sujets amusiques présentaient une cérébrale semblable aux sujets contrôles pour les changements de hauteur,

mais pas pour les changements temporels. Ces résultats suggèrent que les amusiques auraient un déficit de discrimination des changements fins de hauteurs quand ces changements interviennent rapidement. Cette idée est confirmée par les résultats d'une étude comportementale menée chez ces mêmes sujets. Un trouble complexe touchant la perception des intervalles, la direction des hauteurs, et la résolution temporelle contribuerait aux problèmes musicaux des sujets amusiques. Dans la dernière étude de cette thèse, la technique de 'voxel-based morphometry' a été utilisée afin de vérifier l'existence de différences corticales anatomiques entre les sujets amusiques et des sujets contrôles. Les résultats ont démontré une réduction de la quantité de matière blanche dans le gyrus frontal inférieur droit chez les sujets amusiques qui était liée à des déficits de discrimination des hauteurs. Ces données suggèrent que les connections corticales frontales seraient fondamentales pour l'acquisition normale de la musique. Les résultats de cette thèse aident à mieux cerner cette pathologie, et à mieux comprendre les fonctions cérébrales normales et pathologiques. Et notamment, ces résultats montrent quelles sont les régions neuronales essentielles pour un développement musical normal.

Mots clés: amusie congénitale, 'tone-deafness', discrimination des hauteurs et discrimination temporelle, les corrélats comportementaux et neuronaux, le cortex auditif, IRMf, 'voxel-based morphometry'

Abstract

The main objectives of this thesis were to better understand abnormal and normal musical brain development, and to shed light on the brain specialization for music. To these aims, we conducted four studies in which we investigated the behavioral and neural correlates of congenital amusia, a lifelong disability that prevents otherwise normal functioning individuals from developing basic musical skills. Previous evidence has indicated that congenital amusia may be due to a problem in fine-grained pitch discrimination. In the first study, we sought to better detail this pitch deficit and to evaluate its specificity in a group of amusic adults and musically-intact controls. Subjects were presented with monotonic and isochronous sequences of five tones and were required to detect when the fourth tone was displaced in pitch or time. As expected, all amusic participants were impaired in detecting the pitch changes, but performed as controls in detecting the time changes. The results confirm that amusics have a severe and specific deficit in fine-grained pitch discrimination. Moreover, the data point to the presence of a congenital neural anomaly that selectively impairs pitch processing. In order to verify this idea, in study 2, we performed a functional magnetic resonance imaging (fMRI) study to investigate pitch pattern perception in a group of University students with no musical problems. Consistent with previous findings, the right auditory cortex more finely tuned to pitch changes that the left. In study 3, we used fMRI in a similar paradigm to investigate pitch and time discrimination in a group of congenital amusic adults and musically-intact controls. Contrary to expectation, amusics exhibited a similar pattern of activation as controls in processing the pitch sequences, and a deviant pattern of activation in processing the same sequences when they were presented at various temporal rates. These imaging results suggested that amusics have problems to capture fine pitch changes when they are presented rapidly. This idea was confirmed in a subsequent behavioral study. We interpreted these results as amusics having a complex deficit, involving

pitch distance, pitch direction, and temporal resolution that may contribute to the musical impairments observed in congenital amusia. In the final study of this thesis, we employed voxel-based morphometry (VBM) to detect brain anatomical differences in amusic individuals relative to musically-intact controls, in two independent samples of subjects. The results were consistent across samples in highlighting a reduction in white matter concentration in the right inferior frontal gyrus of amusic individuals. This anatomical anomaly was related to pitch-based musical tasks. Thus, the data point to the integrity of white-matter tracts in right frontal brain areas as being key in acquiring normal musical competence. The findings from this thesis serve to further document this disorder, and to better understand both abnormal and normal brain function in terms of which neural regions are essential to normal musical development.

Keywords: congenital amusia, tone-deafness, pitch and time processing, behavioral and neural correlates, auditory cortex, fMRI, voxel-based morphometry

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List of abbreviations

ANOVA	analysis of variance
BA	Brodmann area
BOLD	blood oxygenation level dependent
DTI	diffusion tensor imaging
ERP(s)	evoked related potential(s)
fMRI	functional magnetic resonance imaging
GM	grey matter
HG	Heschl's gyrus
IFG	inferior frontal gyrus
MBEA	Montreal Battery Evaluation of Amusia
MRI	magnetic resonance image
PET	positron emission tomography
PT	planum temporale
rIFG	right inferior frontal gyrus
ROI	region of interest
STG	superior temporal gyrus
STS	superior temporal sulcus
TE	echo time
TR	repetition time
VBM	voxel-based morphometry
VOI	volume of interest
WM	white matter

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Music — The one incorporeal entrance into the higher world of knowledge which comprehends mankind but which mankind cannot comprehend.

Ludwig van Beethoven

GENERAL INTRODUCTION

Music is everywhere. Throughout human history, and across all cultures, humans have produced and enjoyed music (Merriam, 1964). Music is thought to date back 40 000 and 80 000 years, as suggested by the recent discovery of an ancient bone flute (Turk et al., 1996). Today, music constitutes a multi-billion dollar industry world-wide. Thus, music is undeniably ingrained in human culture. Over the past few decades there has been an explosion of research on music and the brain (see Peretz and Zatorre, 2005 for a recent review). This research interest has been motivated by the fact that music offers a unique opportunity to better understand the organization of the human brain. Given that music spans many processing modalities such as the auditory, visual and motor modes, it provides a key means of studying perception, memory, attention, emotion and performance. Moreover, exploring the neural substrates of music helps to shed light on the origin and biological value of music.

While some have argued that music may simply be a recent invention (Pinker, 1997), the universal and ancient quality of music provides a strong counter-claim to this view. Indeed, there is increasing evidence that music has biological foundations (Wallin et al., 2000; Zatorre & Peretz, 2001). This idea is supported by findings from infant studies that the intact human brain seems to be predisposed to music. For example, infants before one year of age have shown exceptional musical abilities that are similar to those of adults (see Trehub, 2001 for a review). Moreover, there is increasing evidence that humans are born with core musical knowledge bases, and that these may be subserved by music-specific neural networks (see Peretz and Hyde, 2003 for a review).

However, about four percent of the general population seem to born without these musical predispositions (Kalmus and Fry, 1980; Drayna, personal communication, cited in Peretz and Hyde, 2003). Such individuals are commonly called 'tone-deaf', and show specific and severe life-long

impairments in both the perception and production of music, despite an otherwise normal functioning. While this condition has been entertained for more than one century (Grant-Allen, 1897; Geschwind, 1984), our laboratory was the first to perform an in depth empirical investigation into this musical disorder, which we refer to as *congenital amusia* (Peretz, 2001; Ayotte et al., 2002). Behavioral evidence from our laboratory has shown that the disorder is specific to music, and largely due to a deficit in pitch processing, while time processing seems to be less affected (Ayotte et al., 2002; Peretz et al., 2003).

Given that this disorder is music-specific, it provides a unique means to investigate the organization of the human brain in general and the neural bases of musical processing in particular. In the present thesis, our main objective was to enrich our current understanding of both abnormal and normal musical brain development. To this aim, here, for the first time, we investigated the functional and structural neural correlates of congenital amusia. Given that previous evidence has shown that it is largely a pitch-based disorder, we first sought to further investigate the severity and specificity of the pitch deficit in amusics at a behavioral level. We then searched for a congenital neural anomaly that we hypothesized to be at the root of this pitch deficit. By examining which neural structures may be compromised in congenital amusia, we can better understand which neural regions are important in acquiring normal musical competence.

We also sought to shed light on the biological foundations of music. One way to do this is to show that the musical system is autonomous from other cognitive functions (such as language for example). If music is indeed a true biological function, and not merely the by-product of another brain function, we expect it to be independent from other cognitive functions. Thus, the existence of a congenital music-specific disorder inherently provides support for this idea. However, it is important to note that music involves different processing components, only some of which appear to be music specific (see

Peretz and Zatorre, 2005 for a review). Given that congenital amusia uniquely impairs music processing, the study of this disorder may help to determine which processing components are exclusive to music and which are not. Thus, the study of its neural correlates may inform us on the brain specialization for music processing.

Evidence that the human brain is predisposed for music

As mentioned above, the notion that music has biological foundations is supported by recent evidence suggesting that the intact human brain is predisposed to music. Indeed, very young infants, before one year of age, exhibit similar musical abilities to those of adults, even before they have acquired language abilities. For example, six-month-old infants are sensitive to dissonance and musical scale structure (Schellenberg and Trehub, 1996; Trehub et al., 1999). Just as adults, infants seem to prefer consonant intervals to dissonant ones, and show learning preferences for musical scales with unequal steps (Schellenberg and Trehub, 1996; Trehub et al., 1999). In the time domain, as adults, four-month-old infants prefer music that has an isochronous temporal pulse, and they are sensitive to slight disruptions in temporal regularity (Drake, 1998).

These infant studies point to the existence of core musical knowledge bases that underlie the development of musical competence. The encoding of pitch along musical scales and the ascribing of a regular pulse to incoming events constitute core musical processing components. These aspects create expectancies and are integral to the hierarchical organization of music (Tillman et al., 2000; Large and Jones, 1999). Moreover, both are likely specialized for music processing. In particular, pitch (tonal) knowledge appears to be unique to music (Jackendoff, 1987). In contrast to speech, in music, pitch variations form a determinate scale (Balzano, 1982). The use of scales is universal and these are formed from a pattern of 5 to 7 focal, unequal-spaced pitches. These pitches are organized around a central tone,

called the tonic (Burns, 1999; Dowling, 1982). In tonal music, there is a hierarchy of importance among the tones, where the non-scale tones are the least related to the musical context and thus often sound anomalous. This tonal knowledge appears to be implicit and thus anyone can detect a wrong note, for example. However, in the case of brain damage, this implicit ability may be compromised or lost.

Indeed, in cases of acquired amusia, which occur consequent to a brain lesion, tonal knowledge may be exclusively disturbed, while pitch discrimination is spared (Peretz, 1993). Such patients can no longer hear the difference between tonal and atonal music, and cannot detect a wrong note in a tonal melodic context. The reverse case also exists, where brain damage results in impaired pitch perception, but spares tonal knowledge (Tramo et al., 1990). These cases suggest that there exists a separable neural network that underlies tonal pitch encoding, that can be selectively impaired or spared by brain damage. Recent evidence from functional neuroimaging points to inferior frontal brain areas as being critically involved in tonal pitch processing (Zatorre et al, 1994; Koelsch et al, 2002; Tillmann et al, 2003).

In addition to the processing of tonal pitch, music memories (Peretz, 1996), and singing (Jeffries et al., 1993; Zatorre and Peretz, 2001) appear to be subserved by music–specific neural substrates. However, the best documented of these are the neural networks of musical recognition. Several cases have been described of brain-damaged patients who are unable to recognize once very familiar melodies, but have no problem to recognize speech and environmental sounds (see Peretz and Hyde, 2003 for a review). The reverse case has also been documented where patients are unable to recognize spoken words, but are still able to recognize music (Godefroy et al., 1991; Mendez, 2001).

Taken together, the evidence from the study of patients with acquired amusia that show either a selective impairment or sparing of music processing, points to the existence of two distinct processing modules: one for music and one for speech (Peretz and Coltheart, 2003). Thus, the existence of these patients that have an exclusive musical impairment consequent to brain damage, supports the idea that there exists music-specific neural networks. As mentioned above, one goal of the present thesis is to gain insight into the brain specialization of music by studying the neural correlates of neurologically intact individuals with music-specific impairments, which we refer to as congenital amusia.

Background of congenital amusia

Congenital amusia is a lifelong disability that prevents otherwise normal functioning individuals from developing basic musical skills (Peretz, 2001; Ayotte et al., 2002). This condition cannot be explained by any acquired brain lesion, hearing problem, cognitive or socio-affective deficit, or lack of musical exposure. This disorder has been variously called tone-deafness, and dysmusia, however, the term congenital amusia better reflects the possibility that there exist as many forms of congenital amusias as they are forms of acquired amusias (Peretz et al, 2002).

The early research on congenital amusia consists of anecdotal case descriptions (Grant-Allen, 1897; Geschwind, 1984). Several epidemiological studies attempted to quantify congenital amusia and to assess its prevalence in the general population (Fry, 1948; Kalmus and Fry, 1980; Drayna, personal communication, cited in Peretz and Hyde, 2003). In these studies, the authors tested a large subset of the general population in the ability to detect a wrong note in popular melodies. The results suggested that about four percent of the general population are amusic. However, these studies suffer from a lack of validity since they considered only one aspect of musical

processing. Nonetheless, these findings converge to show that afflicted individuals have problems in the processing of pitch information.

In an attempt to improve upon these studies, our laboratory recently performed an empirical, in depth investigation to document the presence and nature of congenital amusia (Ayotte et al., 2002). To this aim, we tested a group of eleven congenital amusic adults in a variety of musical and non-musical tests. Despite having above average intellectual, memory and language skills, and normal audiometry, the amusic participants had performance deficits on a standardized battery of musical tests (Peretz et al., 2003). Amusics showed problems in musical recognition, and memory. The deficits were limited to the musical domain, since amusics had no problem to process and recognize speech, including speech prosody, common environmental sounds and human voices.

Most notably, amusics showed problems in musical pitch perception, while time perception was less affected (Ayotte et al., 2002; Peretz et al, 2003). Their pitch-based deficit was most notable when amusics were required to detect "a wrong note" (out-of-scale note) in a conventional melody (Ayotte et al., 2002). Thus, it seems that amusics do not have the tonal knowledge necessary to map pitches onto musical scales. Given that there was no overlap between the distributions of the amusics' and controls' scores, this test was considered to be diagnostic. This point is especially interesting, since a recent twin study has shown that the ability to detect a wrong note in a popular melody may be heritable (Drayna et al., 2001). Thus, amusics appear to lack a key pitch processing component that is specific to music, and which appears to be genetically transmittable. Such a musical pitch processing deficit is thought to lend to the myriad of musical impairments seen in congenital amusia. However, this deficit may originate from a more basic problem in fine-grained pitch discrimination.

Congenital amusia: a fine-grained pitch-based disorder

This possibility was motivated by recent findings of a severe deficit in fine-grained pitch discrimination in one particular amusic individual that has been tested extensively in our laboratory (Peretz et al., 2002). As mentioned above, one goal of the present thesis was to investigate the severity and specificity of this acoustic pitch deficit in a group of congenital amusic adults. At the time of publication of our study (study 1 of this thesis; Hyde and Peretz, 2004), another group working on the same topic, published work showing that, indeed, a group of congenital amusic adults had a fine-grained pitch deficit (Foxton et al., 2004). It is plausible that such an acoustic deficit may be at the root of congenital amusia. For example, the correct internalization of musical scales depends on fine-grained pitch perception since scales use small pitch intervals of 1 or 2 semitones (corresponding to 1 or 2 adjacent keys on a keyboard). Western melodies (Vos and Troost, 1989) and other world music (Dowling and Harwood, 1986) are constructed with such small pitch distances. Thus, the inability to detect small pitch changes may lend to problems in musical pitch processing. One important implication of this idea is that fine-grained pitch perception may be essential for the normal development of musical abilities. Since amusics are likely born with such an acoustic pitch deficit, they would never have acquired the implicit tonal knowledge required for normal musical competence.

While pitch is clearly essential to the musical domain, it also plays an important role in speech communication. For example, in tonal languages such as Mandarin, Thai and Vietnamese, pitch is used to alter the meaning of words. In non-tonal languages, a final rising pitch is key to signal a question. However, congenital amusics have no problem to distinguish these variations in pitch intonation (Ayotte et al., 2002). This is due to the fact that language employs much coarser pitch variations than does music (Fitzsimons et al., 2001). Thus, a problem in basic pitch discrimination may solely compromise the musical domain and not language, not because it is music-specific, but

due to the fact that music utilizes more fine-grained pitch changes. From this perspective, congenital amusia may be due to an acoustic pitch deficit that is not music-specific, but merely music-relevant. As mentioned above, one major goal of the present thesis was to investigate the neural correlates of such a pitch deficit in congenital amusia. In order to evaluate the specificity of the pitch deficit at a neural level, we also considered temporal processing.

Neural correlates of congenital amusia

Neural basis of pitch and time discrimination

Given the evidence that amusics have a pitch deficit, it is plausible to expect that amusics have a congenital brain anomaly that selectively impairs sequential pitch processing. Other than the work reported in the present thesis, there has been only one study from our laboratory to investigate the functional neural correlates of congenital amusia (Peretz et al., 2005). In this study, an event-related potential (ERP) method was used to narrow down the locus of a possible neural anomaly in amusics. Subjects were required to detect a rare deviant tone in a sequence of repetitive standard tones while their ERPs were recorded. Amusics showed no brain response to pitch deviances smaller than one semitone, whereas controls did so consistently. In contrast, amusics showed an enlarged brain response to large pitch changes of 2 and 3 semitones, with an N2 (that was not present in controls) and a P3 almost twice as large as that observed in controls. These abnormal brain responses were inferred to be neural markers of the amusics' fine-grained pitch processing deficit. Given the limited spatial resolution of the ERP approach, it was not possible to localize the exact brain areas of these abnormal responses. However, the electrical activity of the auditory cortex of amusic individuals appeared to be intact as indexed by a normal N1 response (Peretz et al., 2005).

This finding was somewhat surprising. Given that congenital amusia is largely a pitch-based disorder, we expected to find a neural anomaly in the

right auditory cortex, a region known to be implicated in musical pitch processing. For example, studies of brain-lesioned patients have shown that the right auditory cortex is critical in the perception of missing fundamental pitch (Zatorre, 1988), in discriminating melodic (pitch) contours (Peretz, 1990), in perceiving the direction of pitch change (Johnsrude et al., 2000), and in using melodic contextual cues in pitch judgments (Warrier and Zatorre, 2004). Consistent support comes from neuroimaging studies showing a preferential role of the right auditory regions in the processing of melodies (Zatorre et al., 1994; Patterson et al., 2002), in the maintenance of pitch while singing (Perry et al., 1999), imagery for tunes (Halpern and Zatorre, 1999), and in the detection of deviant chords (Tervaniemi et al., 2000). It is possible that a pitch-based neural anomaly does exist in the right auditory cortex of amusics, but that it is merely too subtle to be detected with the ERP technique. In the present thesis, we used functional magnetic resonance imaging (fMRI) as a more sensitive means to uncover a possible neural anomaly in the auditory cortex of the amusic brain, since fMRI has a greater spatial resolution relative to the ERP method.

In order to localize a possible neural anomaly in the auditory cortex of amusic individuals it is important to describe the structural and functional organization of the auditory cortex. Microelectrode and tracer studies in the auditory cortex of nonhuman primates serve as an excellent model for understanding the neuroanatomy of the human auditory cortex. The macaque auditory cortex is composed of a central core, a surrounding belt, and a lateral parabelt (Hackett et al., 1998), and this cortical system is connected hierarchically (Kaas and Hackett, 2000). A recent comparative study of the auditory cortex in macaques and humans (Hackett et al., 2001) suggests that the human auditory cortex also consists of a core or primary auditory region (localized in the medial portion of Heschl's gyrus) that is surrounded by belt and parabelt regions corresponding to secondary auditory cortices, and that these structures are connected in a hierarchical fashion. Recent fMRI

evidence has shown that there is a hierarchy of pitch processing in humans with the activation moving anterolaterally as processing proceeds (Patterson et al, 2002). Pitch extraction is thought to be completed in primary auditory cortex; whereas higher-level processes like pitch tracking and melody extraction are thought to be performed in more distributed regions beyond primary auditory cortex, and the processing becomes asymmetric with more activity in the right hemisphere (see Zatorre et al., 2002 for a review). On the basis of the behavioral evidence showing that amusics have a deficit in pitch discrimination (Hyde and Peretz, 2004; Foxton et al., 2004), we hypothesized that amusics may have a pitch-based neural anomaly in the right primary auditory cortex.

Given that congenital amusia has been found to primarily be a pitch-based deficit, most of the research into congenital amusia to date has been concentrated on pitch processing. Consequently, there has been less focus on the temporal aspects of this condition. To our knowledge, no study has systematically investigated how amusic individuals process temporally changing pitch information. To understand how the amusic brain processes temporal pitch changes, it is first important to review which brain structures are known to be implicated in these processes. Collective evidence shows that left auditory regions seem to be preferentially involved in fine temporal resolution. For example, findings from studies of brain-lesion patients (Phillips & Farmer 1990; Tallal et al, 1993; Ehrlé et al., 2001) single-unit-electrode recordings (Liégeois-Chauvel et al., 1999), auditory steady-state electrophysiological data (Yamasaki et al., 2005) and neuroimaging data (Belin et al., 1998; Zatorre and Belin, 2001; Schönwiesner et al., 2005), have shown that left auditory cortical regions play a critical role in rapid temporal processing. Thus, in the normal brain, the right auditory cortex appears to play a preferential role in fine-grained pitch perception and the left, in fine temporal discrimination. Zatorre and colleagues have recently proposed that the auditory system has developed this relative hemispheric asymmetry so as

to optimally process incoming simultaneous spectral and temporal acoustic information from the environment (Zatorre et al, 2002). In the present thesis, we sought to determine whether the amusic brain shows this typical hemispheric asymmetry in the processing of pitch and time information.

Structural neural correlates

In addition to the functional neural underpinnings of congenital amusia, we also sought to investigate the neuroanatomical correlates of this condition. In a previous case study of a severely impaired amusic individual (Monica), we did not find any structural neural anomalies by visual inspection of her MRI brain image (Peretz et al., 2002). However, the brain anomaly in amusics may be very subtle, and thus would explain why we were previously unable to detect an anomaly in the case of Monica by mere visual inspection. The notion that we may expect to find a structural neural anomaly in the congenital amusic brain is motivated by findings of structural brain differences in a variety of other developmental disorders. For example, individuals affected by a severe speech and language disorder were recently found to have reduced grey matter in speech and motor-related regions (Watkins et al., 2002). In another study, developmentally dyslexic adults were shown to have a structural grey matter deficit involving a complex fronto-temporal network thought to be implicated in phonological processing (Vinckenbosch et al., 2005). Still another study revealed that autistic children had significant decreases of grey matter concentration in the superior temporal sulcus bilaterally, a region implicated in social perceptual skills that are characteristically impaired in autism (Boddaert et al., 2004). In the above three studies, a computerized brain morphometric analysis technique known as voxel-based-morphometry (VBM) was used to compare brain tissue concentrations between groups (Ashburner et al., 2000). VBM is a method of choice since it allows an exploratory search throughout the brain for relationships between a behavioral measure and brain morphology. VBM is an automated technique and thus eliminates the rater-bias in the manual

identification of anatomic boundaries. In addition, with VBM, it is possible to examine white matter morphology, which is otherwise difficult due to the lack of clear boundaries between adjacent white matter subregions. For these reasons, in the present thesis, we chose to use VBM to search for structural brain differences between amusics and musically-intact controls.

The combination of behavioral, functional and structural investigations into the neural correlates of congenital amusia provides a powerful means to better understand abnormal and normal musical brain development. Moreover, this approach helps to shed light on the biological origins of music and the brain specialization for music.

Research hypotheses

To these aims, in the present thesis, we put forth three main hypotheses.

First, on the basis of a single case, Monica, we hypothesized that congenital amusia may be due to a basic deficit in pitch discrimination. We expected this pitch deficit to be severe and specific to the pitch domain. Accordingly, we predicted that amusics would have problems to detect pitch changes in an otherwise monotonic tone sequence, but retain the ability to detect temporal changes in the same sequence.

Next, we hypothesized that amusic individuals would show a deviant pattern of brain activity relative to musically-intact controls in the processing of pitch patterns. We expected to find differences in brain activation between these two groups specifically in the right auditory cortex, since this area is known to play a key role in pitch processing. In contrast, we did not expect to find any differences in brain activation between amusics and controls in terms of temporal processing of the same pitch patterns.

Finally, we expected to find structural brain differences between amusic

individuals and musically-intact controls. In particular, we expected to find a structural neural anomaly in the right auditory cortex of amusic individuals, given the role of this structure in pitch processing.

In order to test these hypotheses, we conducted four studies using various approaches including psychophysics and both functional and structural neuroimaging. We first performed a behavioral study to investigate pitch and time discrimination in a group of congenital amusics adults and musically-intact controls. We next conducted an fMRI study to investigate the neural basis of pitch pattern processing in a group of musically-intact university students. Using a similar paradigm, we then used fMRI to investigate the neural correlates of pitch and time discrimination in a group of amusic adults and controls. Lastly, we employed VBM to search for any structural neural anomaly in the form of brain matter concentration differences in the amusic brain relative to controls.

FIRST ARTICLE:
BRAINS THAT ARE OUT OF TUNE BUT IN TIME

Brains That Are Out Of Tune But In Time

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Abstract

It is estimated that about 4% of the general population may be afflicted with amusia (or tone-deafness). Congenital amusia is a lifelong disability for processing music despite above-average intellectual, memory, and language skills. Here we present evidence that the disorder stems from a deficit in fine-grained pitch perception. Amusic and control adults were presented with monotonic and isochronous sequences of five tones (i.e., constant pitch and inter-tone interval). They were required to detect when the fourth tone was displaced in pitch or time. All amusic participants were impaired in detecting the pitch changes, and showed no sign of improvement with practice. In contrast, they performed as controls in detecting the time changes and exhibited similar improvements with practice. Thus, amusics' poor pitch perception cannot be ascribed to nonspecific problems with the task nor to poor hearing in general. Rather, the data point to the presence of a congenital neural anomaly that selectively impairs pitch processing.

Humans appear to be born musical. Before one year of age, infants display remarkable perceptual abilities that are similar, in many respects, to those of adults. In particular, infants show enhanced processing for scales with unequal pitch steps (Trehub, Schellenberg & Kamenetsky, 1999) and for regular rhythms (e.g., Bergeson, 2002). These initial preferences for encoding pitch along musical scales and for ascribing a regular pulse to incoming events are essential to the hierarchical organization of music. This type of organization facilitates music processing by creating expectancies and feelings of surprise or satisfaction. The fact that these skills appear precociously, well before they have obvious utility, is consistent with the proposal of music-specific predispositions (Trehub, 2001).

Some individuals appear to lack such predispositions for music. Their musical failure cannot be explained by low intelligence nor environmental circumstances (e.g., hearing impairment, lack of stimulation). For example, Che Guevara (the highly educated revolutionary) and Milton Friedman (Nobel Prize in Economics) reported life-long musical handicaps despite having taken music lessons in childhood (Taïbo, 1996; Friedman, 1998). The prevalence of this disorder, which we term congenital amusia (Peretz et al., 2002), has been estimated at about 4 % in the UK (Kalmus & Fry, 1980) and about 5 % in the USA (Drayna, personal communication). However, these estimates are based upon performance on a single measure of musical ability, which may have both poor validity and poor reliability. This may explain why most researchers and educators do not consider amusics as genuine anomalies, but rather as "drop-outs" of music-education systems that favor the musical elite (Kazez, 1985).

Recent evidence suggests that congenital amusia is a real disorder (Ayotte, Peretz & Hyde, 2002; Peretz et al., 2002). According to a basic neuropsychological principle, a slight but congenital neural deviation may produce selective learning deficits. Thus, we searched for individuals afflicted

with lifelong musical difficulties in order to study them in detail. From a large pool of 45 volunteers with confirmed musical disorders on objective testing, we selected the most clear-cut 11 cases and were able to document, across multiple tests, that their deficit in discriminating and memorizing music was a genuine learning disability. Their music disorder was remarkably selective. Language was intact, including the recognition of song lyrics and of speech intonation. Moreover, the processing of rhythm was much less affected than that of pitch. Specifically, the only test on which all 11 amusic participants failed to obtain normal scores was a pitch-based test, similar to that used in the large prevalence surveys mentioned above. The test required listeners to detect the presence of an anomalous note (i.e., played on a pitch that is out-of-scale) in conventional melodies. Amusics seem to lack the musical predisposition for encoding pitch in terms of musical scales.

Nonetheless, the musical deficiency might arise from a more elemental defect. This hypothesis was suggested by the discovery of a deficit in basic pitch discrimination in our first documented case of congenital amusia, Monica (Peretz et al., 2002). Monica could barely detect a rising pitch change as large as 2 semitones. The semitone is the smallest pitch distance represented by two adjacent keys on a keyboard and is well above the limit of normal pitch acuity, which lies in the order of a quarter of a semitone (e.g., Olsho, Schoon, Sakai, Turpin, & Sperduto, 1985). Moreover, Monica could barely perceive falling pitch changes across a wide range of pitch distances. This peculiar and systematic defect points to the presence an aberrant pitch perception system.

The presence of an inborn and basic defect in pitch perception may well account for the emergence of a lifelong musical impairment. Poor pitch perception is likely to prevent the normal internalization of musical scales that have steps between consecutive notes of 1 or 2 semitones. Most Western melodies are constructed with small pitch distances between consecutive

tones; 70 % are 0 (repeated pitches), 1, or 2 semitones in size (Vos & Troost, 1989). Similar pitch size distributions are observed across musical styles and cultures (Dowling & Harwood, 1986). In short, a perceptual system that is unable to detect small pitch changes is likely to miss an essential part of musical structure.

The goal of the present study was to assess the generality of this account. We tested a group of 10 congenital amusic individuals and matched controls in tasks that required basic pitch and temporal discrimination. The participants heard "standard" sequences of five piano tones presented monotonically (constant pitch) and isochronously (constant inter-tone interval), as well as "comparison" sequences in which the fourth tone was displaced in pitch or time. Their task was to detect a change to the fourth tone of a sequence. We expected amusic individuals to experience difficulties on the pitch dimension to a greater extent than on the time dimension.

Method

Participants

The amusic group consisted of eight adults who had participated in a previous study (Ayotte et al., 2002) and two new volunteers. As can be seen in Table 1, there is a high proportion of aged female participants, as is generally the case in educated volunteers. Each amusic individual was matched in age, gender, education, and handedness to a normal control participant (four from Ayotte et al., 2002, and six new recruits) with no formal musical. None of the participants had any previous neurological or psychiatric history.

Objective testing confirmed the presence of a musical deficiency in the amusic participants, who scored significantly below matched controls in two series of tests taken from the Montreal Battery of Evaluation of Amusia (MBEA; http://www.fas.umontreal.ca/psy/iperetz.html; see Table 1). The

battery involves six tests, four of which are presented here. Three of these assess the ability to discriminate changes in melody (by pitch contour, scale, and interval size) and one tests rhythmic discrimination (by temporal grouping). Both the melodic and rhythmic tests use a "same-different" discrimination task, with the same set of novel but conventional sounding music. Average group results for both amusics and controls are summarized in Table 1. Examination of individual data indicates that each amusic participant was impaired in the melodic tests, while about half of them showed normal performance in the rhythmic test. To illustrate the domain-specificity of their disorder, scores obtained on a recognition task of familiar spoken lyrics and of the corresponding song tunes (without lyrics) are also presented. Further test details can be found in Ayotte et al., 2002.

-Insert table 1 about here-

Stimuli, apparata and procedure

Stimuli consisted of 21 different sequences, each containing 5 successive tones. In the "standard" sequence, all tones were 100 ms long, played at the pitch level of C6 (1047 Hz) and synthesized with a piano timbre (on a Roland SC 50 sound canvas) with the inter-tone-onset interval (ITI) set to 350 ms. When a sequence differed from monotony or isochrony, its fourth tone was altered. In the 10 pitch-altered sequences, the fourth tone was displaced upward or downward in pitch from C6 by one of five pitch distances, ranging from 25 to 300 cents (where 100 cents corresponds to 1 semitone). In the 10 time-altered sequences, the fourth tone was displaced in time from its isochronous position occurring earlier or later by one of five temporal increments that ranged from 8 to 16% of the ITI.

Participants were tested individually in the pitch and time tasks in separate sessions. In both tasks, they were asked to press a " yes " button whenever they detected a change and a " no " button when they were unable to detect a

change. Trials were randomized and half contained no change (i.e., the standard monotonic, isochronous sequence), but participants were informed about the nature and the location where a change could occur. They also received 40 practice trials with feedback after each trial. Each test session comprised 360 sequences (180 standards, 18 of each of 10 altered sequences). In order to assess for a possible learning effect, eight amusic and six control participants were presented with an additional series of 240 trials in the pitch task.

The stimuli were presented bilaterally through Sennheiser HD450 headphones in a quiet room, at an intensity level of 70 dB SPL-A.

Results

The percentage of hits (corresponding to a "yes" response when there was a change) minus false alarms (i.e., "yes" response when there was no change) was computed for each participant as a function of the type, direction and size of change.

An analysis of variance, using a 2 groups x 2 directions x 5 distances mixed design, was computed on the data obtained in the pitch task. It revealed a highly significant interaction between Group and pitch Distance, with $F(4, 72)= 95.4$, $p <. 0001$, and no main effect of pitch direction, and no interactions involving pitch direction ($F<1$). Since pitch direction did not influence performance, the scores presented in Figure 1 are averaged for upward and downward pitch changes. As can be seen, the amusic group detect pitch changes of 200 cents and above as well as normals, but exhibit difficulties at smaller distances. They perform below normal controls at 100 cents ($t18 = 2.32$, $p < .05$). While the pitch impairment was observed in each amusic individual, controls obtained perfect scores over all pitch distances.

In contrast, in the time change detection task, the amusics' performance matches that of normal controls, even at subtle time differences (Figure 1b). The ANOVA revealed no Group effect ($F(1, 18)= 2.9$, $p > .10$) nor significant interaction with temporal Distance ($F<1$) nor with time Direction (early versus late; $F<1$).

As shown in Figure 2, the amusic participants show no clear improvement over blocks (each comprising 120 trials) in the pitch task. In contrast, they seem to benefit from prior experience as much as controls in the time task. The data obtained in the first three blocks of trials were submitted to an overall ANOVA, considering Group, Task and Block as factors in a mixed design. It revealed a significant interaction between the three factors, with $F(2,36)= 9.6$, $p < .001$. This reflects the fact that the only condition in which performance declines rather than improves over blocks of trials is found in the pitch task by the amusic participants. The decline was significant, with $F(2,18)=4.3$, $p<.03$. Performance significantly improved with practice in all other conditions ($F(2,18)=89.56$, $p<.001$ for amusics in the time task; $F(2,18)=4.3$ and 10.77, $p<.03$, for controls in the pitch and time task, respectively).

-Insert Figures 1 and 2 about here-

Discussion

The results confirm the presence of a basic pitch defect in individuals suffering from congenital amusia. Amusics have difficulty detecting changes in pitch that are smaller than two semitones (200 cents), while normal acuity is at least four times more fine grained. Lack of task understanding or auditory attention problems cannot account for the deficit since amusics are able to detect large pitch changes (over two semitones). The disorder also appears to be irreversible because practice impairs rather than facilitates pitch judgments. Finally, the disorder is specific to pitch processing. When the

change to be detected involved a time deviation from synchrony, rather than a pitch deviation from monotony, amusics were as accurate as controls. They obtained thresholds conform to typical values, with 75% of correct detection for an asynchrony of about 40 ms (Ehrlé, Samson & Baulac, 2001; Hirsh, Monahan, Grant, & Singh, 1990; Schulze, 1989). Thus, the results provide compelling evidence that amusic adults have an impaired ability to discriminate pitch changes.

Although the pitch defect is less severe in the present sample of amusic participants than in our first case, Monica, it was found to interfere with the discrimination of the crucial musical interval of one semitone. Moreover, the problem was revealed in the context of a single repeating tone. When additional uncertainty is added -as in a musical context- the same defect is likely to be greatly amplified. Given that amusics are probably born with this deficit, they have likely never assimilated the structure of musical scales nor acquired the sophisticated tonal knowledge that every normally developing individual builds on scales, albeit implicitly (Tillman, Bharucha & Bigand, 2000).

The importance of pitch for the musical domain is obvious. However, pitch also contributes to speech communication. Yet, amusic individuals have no problem to detect pitch changes in speech intonation (Ayotte et al., 2002). This is because pitch variations in speech are very coarse as compared to those used in music. For example, the final pitch rise that signals a question is typically larger than 7 semitones in both French and English (e.g., Fitzsimons, Sheahan & Staunton, 2001). Hence, a deficient pitch perception system may compromise music perception exclusively, not because it is specialized for that domain, but because music requirements are more fine-grained.

Music is organized temporally as well as in pitch. As shown here, amusic individuals seem to be able to perceive a regular pulse just as normals. Thus, they should be able to keep time to music by tapping or dancing. However, most amusics report difficulties with these activities. Moreover, about half of them are impaired in rhythmic discrimination of musical excerpts. One possibility is that an ensemble of musical deficits can be evident as cascade effects of a faulty pitch-processing system. In fact, in all previous tests that probed the ability to process temporal structure in a musical context (Ayotte et al.; 2002, Peretz et al., 2002), pitch variations were present. It is possible that pitch variations create noise in the processing system of amusic listeners, hence preventing them from extracting temporal structure and regularity in a reliable manner. As shown here, when no pitch variations are present in the auditory pattern, amusic timing skills seem normal.

To conclude, congenital amusia is best understood as a developmental disorder that arises from failures to encode pitch with sufficient resolution to allow the acquisition of the core knowledge regarding the pitch structure of music. This conclusion implies that, initially, the disorder is not specific to music but is rather related to a more general, psychoacoustic difficulty in fine pitch resolution. Hence, one may consider congenital amusia as a mirror image of some developmental disorders of language. Indeed, some individuals suffer from language-specific disorders that seem to result from a difficulty to hear fine acoustic temporal variations (e.g.,Tallal, Miller & Fitch, 1993). From this perspective, pitch might be to music what time is to speech (Zatorre, Belin & Penhune, 2002).

References

Ayotte, J., Peretz, I., & Hyde, K. (2002). Congenital amusia : A group study of adults afflicted with a music-specific disorder. Brain, 125, 238-251.

Bergeson, T. R. (2002). Perspectives on music and music listening in infancy. Unpublished doctoral dissertation, University of Toronto.

Dowling, W., & Harwood, D. (1986). Music cognition. New York: Academic Press.

Ehrlé, N., Samson, S., & Baulac, M. (2001). Processing of rapid auditory information in epileptic patients with left temporal lobe damage. Neuropsychologia, 39, 525-531.

Fitzsimons, M., Sheahan, N., & Staunton, H. (2001). Gender and the integration of acoustic dimsensions of prosody: Implications for clinical studies. Brain & Language, 78, 94-108.

Friedman, M. (1998). Two lucky people. Memoirs. University of Chicago Press.

Hirsh, I. J., Monahan, C. B., Grant, K. W., & Singh, P. G. (1990). Studies in auditory timing: 1. Simple patterns. Perception and Psychophysics, 47(3), 215-226.

Kalmus, H., & Fry, D. B. (1980). On tune deafness (dysmelodia) : Frequency, development, genetics and musical background. Annals of the Human Genetics, 43, 369-382.

Kazez, D. (1985). The myth of tone deafness. Music Educators Journal, 71, 46-47.

Olsho, L., Schoon, C., Sakai, R., Turpin, R., & Sperduto, V. (1982). Auditory frequency discrimination in infancy. Developmental Psychology, 18(721-726).

Peretz, I., Ayotte, J., Zatorre, R. J., Mehler, J., Ahad, P., Penhune, V. B., & Jutras, B. (2002). Congenital amusia : A disorder of fine-grained pitch discrimination. Neuron, 33, 185-191.

Schulze, H.-H. (1989). The perception of temporal deviations in isochronic patterns. Perception & Psychophysics, 45, 291-296.

Taibo, P. I. (1996). Ernesto Guevara. Tambien cognocido como el Che (4th ed.). Buenos Aires: Planeta.

Tallal, P., Miller, S., & Fitch, R. H. (1993). Neurobiological basis of speech: a case for the preeminence of temporal processing. Annals of the New York Academy of Science, 682, 27-47.

Tillmann, B., Bharucha, J. J., & Bigand, E. (2000). Implicit learning of tonality: a self-organizing approach. Psychological Review, 107, 885-913.

Trehub, S. E. (2001). Musical predispositions in infancy. Annals of the New York Academy of Science, 930, 1-16.

Trehub, S.E., Schellenberg, E.G., & Kamenetsky, S.B. (1999). Infants' and adults' perception of scale structure. Journal of Experimental Psychology Human Perception and Performance, 25, 965-75.

Vos, P. G., & Troost, J. M. (1989). Ascending and descending melodic intervals: Statistical findings and their perceptual relevance. Music Perception, 6(4), 383-396.

Zatorre, R. J., Belin, P., & Penhune, V. B. (2002). Structure and function of auditory cortex: Music and speech. Trends in Cognitive Sciences, 6, 37-46.

Table 1:

Characteristics	Amusic* (n=10)	Control (n=10)	t- test
Age (yrs)	57 (1.6)	58 (1.7)	*n.s.*
Gender	3 M, 7 F	3 M, 7 F	
Education (yrs)	15 (0.6)	17 (0.7)	*n.s.*
Musical discrimination			
Melodic (MBEA)	59.8 (2.3)	88.1 (2.9)	$p < .001$
Rhythmic (MBEA)	71.9 (4.9)	90.4 (3.6)	$p < .05$
Song memory recognition			
Melodies	63.1 (3.5)	**84.8 (2.2)	$p < .001$
Lyrics	90.5 (1.6)	**88.0 (1.7)	*n.s.*

Characteristics of participants, mean percentages of correct responses on key musical tests, and significance levels on corresponding *t*-tests. Standard deviations are in parentheses.

* including A2, A3, A4, A7, A8, A9, A10, and A11 from Ayotte et al., 2002

**Data are from 20 different controls taken from Ayotte et al., 2002.

Figure legends:

Figure 1: Performance in the pitch (panel a) and time (panel b) discrimination tasks, expressed as a mean percentage of hits minus false alarms for each group of participants. Error bars represent standard error.

Figure 2: Performance by block of 120 trials in the pitch (panel a) and time (panel b) discrimination tasks, expressed as a mean percentage of hits minus false alarms for each group of participants. Error bars represent standard error. Eight amusic and six control participants were further tested in block 4 and 5.

Figure 1:

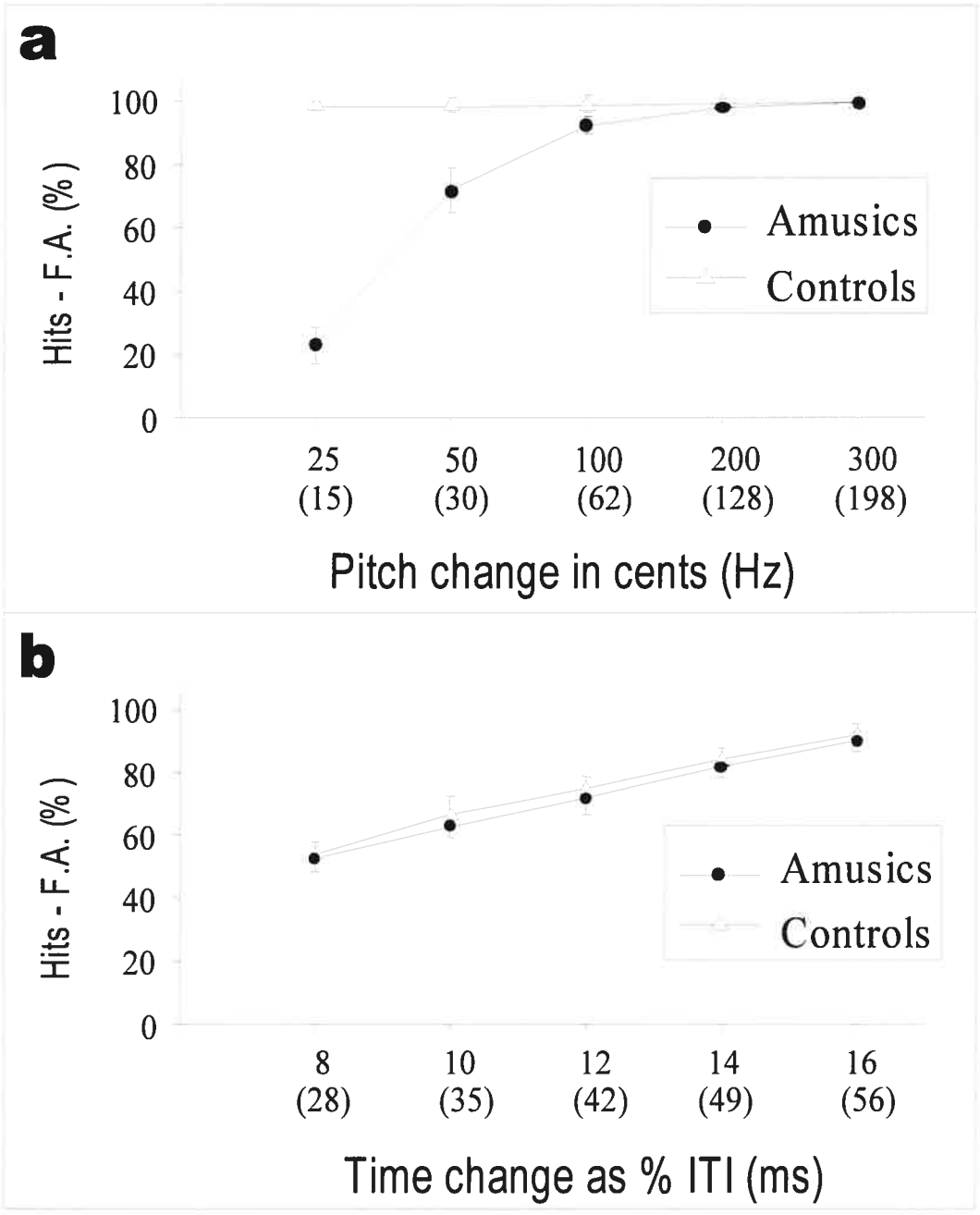
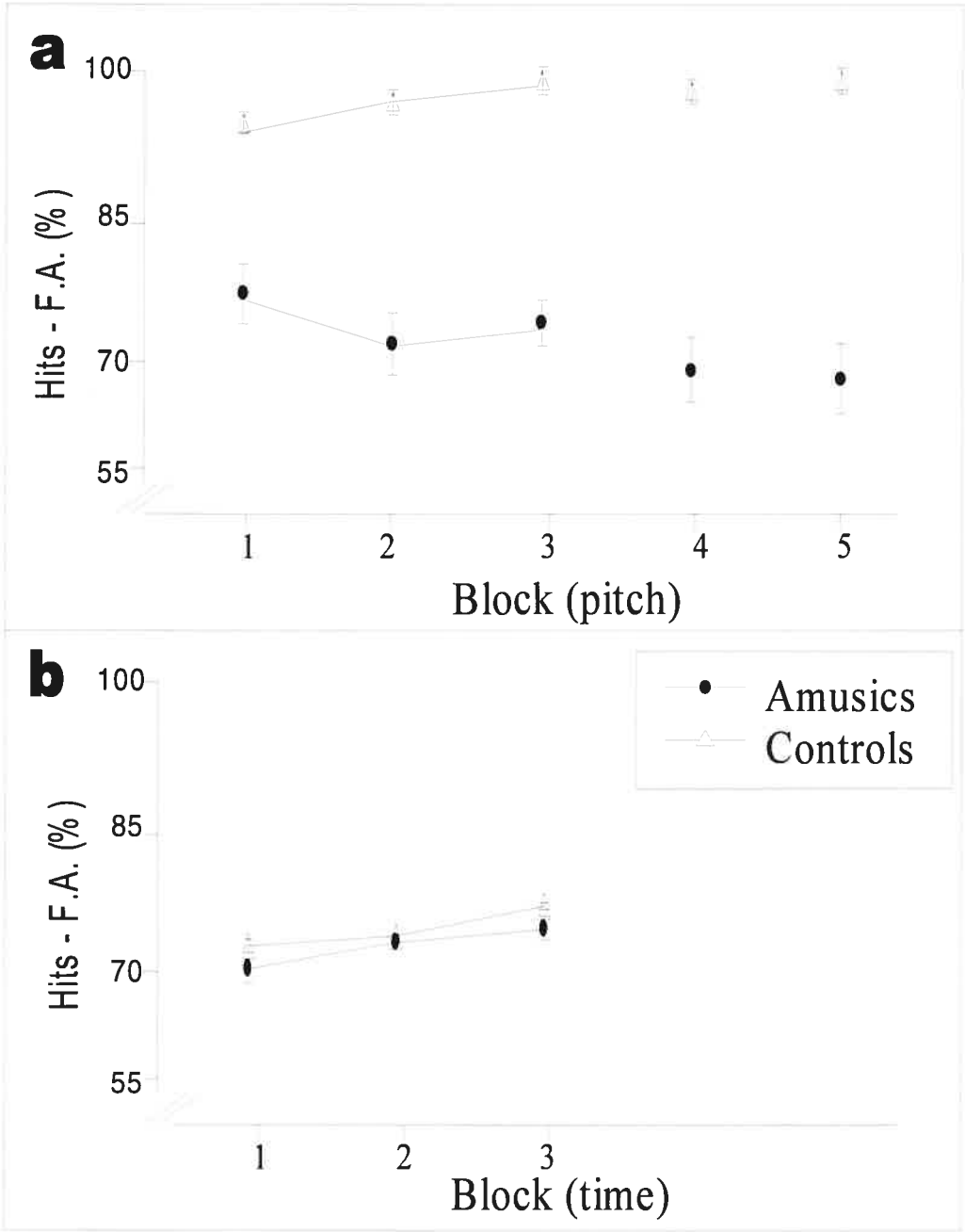

a
100
80
60
40
20
0
Hits - F.A. (%)
Amusics
Controls
25
(15)
50
(30)
100
(62)
200
(128)
300
(198)
Pitch change in cents (Hz)
b
100
80
60
40
20
0
Hits - F.A. (%)
Amusics
Controls
8
(28)
10
(35)
12
(42)
14
(49)
16
(56)
Time change as % ITI (ms)

Figure 2:


a
100
85
70
55
Hits - F.A. (%)
1
2
3
4
5
Block (pitch)
b
100
85
70
55
Hits - F.A. (%)
1
2
3
Block (time)
Amusics
Controls

SECOND ARTICLE:
EVIDENCE FOR THE SPECIFIC ROLE OF THE RIGHT AUDITORY CORTEX IN FINE PITCH RESOLUTION

Evidence for the Specific Role of the Right Auditory Cortex In Fine Pitch Resolution

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Abstract

The neural basis of human pitch perception is not fully understood. It has been argued that the auditory cortices in the two hemispheres are specialized, such that certain right auditory cortical regions have a relatively finer resolution in the frequency domain than homologous regions in the left auditory cortex, but this concept has not been tested directly. Here, we used functional magnetic resonance imaging (fMRI) to test this specific prediction. Healthy volunteers were scanned while passively listening to pure-tone melodic patterns in which the pitch distance between consecutive tones was varied in a parametric fashion. As predicted, brain activation in a region of right lateral auditory cortex was linearly responsive to increasing pitch distance. Whereas this right auditory cortical area was sensitive to even fine pitch changes, the homologous left cortical region was minimally responsive except to large pitch changes. The results support the model of relative hemispheric specialization and provide direct evidence that the right secondary auditory cortex has a finer pitch resolution than the left.

Introduction

Pitch perception is key in the processing of music, a uniquely human attribute, but its neural correlates are not fully understood. Many findings have shown that musical pitch processing preferentially involves right auditory cortical structures. For example, studies of brain-lesioned patients have shown that the right auditory cortex is critical for melody discrimination (Milner, 1962), perception of missing fundamental pitch (Zatorre, 1988), perception of melody in terms of its global contour (Peretz, 1990), direction of pitch change (Johnsrude et al., 2000), and in using melodic contextual cues in pitch judgments (Warrier and Zatorre, 2004). Consistent evidence comes from neuroimaging studies showing that right auditory regions are central in various aspects of musical pitch processing, such as in melodic processing (Patterson et al., 2002; Zatorre et al., 1994), in the maintenance of pitch while singing (Perry et al., 1999), and in imagery for tunes (Halpern and Zatorre, 1999). In contrast, left auditory regions seem to be specialized for rapid temporal processing as required in speech (e.g. Belin et al., 1998; Phillips & Farmer, 1990).

Zatorre and colleagues (2002) have recently proposed that the auditory system has developed two parallel and complementary systems, one in each hemisphere, specialized for differential resolution in the spectral and temporal domains, as a need to optimally process incoming simultaneous spectral and temporal acoustic information from the environment. A similar proposition has been made by Poeppel and colleagues (2003), who suggested that different time integration windows characterize the left and right auditory cortices. Support for this model comes from neuropsychological (Robin et al., 1990), electrophysiological (Liegeois-Chauvel et al., 2001) and neuroimaging studies (Boemio et al., 2005; Brechmann et al., 2005; Schönwiesner et al., 2005; Zatorre and Belin, 2001). In the study by Zatorre and Belin (2001), which was used as a model for the present study, normal subjects were

scanned while passively listening to pure-tone sequences that varied parametrically either in terms of spectral complexity or temporal rate. Responses to the spectral features were weighted towards right auditory areas, whereas responses to the temporal features were weighted towards the left. These findings were interpreted as reflecting that the right auditory cortex has a finer spectral resolution, whereas the left has a higher temporal resolution, but this explanation was not tested directly, and it has not been universally accepted (Scott & Wise 2004).

Here, we used functional magnetic resonance imaging (fMRI) to test the prediction arising from the hemispheric specialization hypothesis that the right auditory cortex is more sensitive to small spectral changes as compared to the left. Subjects were scanned while passively listening to pure-tone melodic patterns in which the pitch distance between consecutive tones was varied in a parametric fashion. We reasoned that if the right auditory cortex has a higher resolution for spectral change, then it should show correlated changes in activity as a function of even small changes in the pitch of a tone sequence; the left auditory cortex, should respond either minimally, or only to larger pitch changes.

Methods

Subjects

Ten healthy right-handed volunteers (half of each gender; mean age 25.3, SD 4.4 years) participated in the fMRI experiment. All had normal hearing as determined via standard audiometric testing and had no formal musical training. All subjects gave informed written consent for a protocol approved by the Montreal Neurological Institute Ethics Review Board.

Behavioral experiment

Prior to scanning, subjects were tested in a pitch discrimination task to ensure that they could discriminate the pitch changes used in the subsequent fMRI experiment. The task was based on one used in a previous study (Hyde and Peretz, 2004). However, here, we used smaller pitch distances. Subjects were presented with a series of 360 five-tone isochronous sequences, where all tones were 100 ms in duration with 250 ms between tones. On half of the trials, all five tones were of the same pitch (1046 Hz), but on the other half, the fourth tone was altered by either a rise or fall in pitch at one of the following distances: 6.25, 12.5, 25, 50, 100, or 200 cents (where 1 cent is a unit of equal log frequency separation; 1 semitone = 100 cents). Subjects were asked to press a " yes " button whenever they detected a change and a " no " button when they were unable to detect a change. The stimuli were presented bilaterally through Sennheiser HD450 headphones in a quiet room, at an intensity level of 70 dB SPL-A in a random order. The test lasted about 10 minutes.

The performance of the ten subjects in the pitch discrimination task as a function of pitch change is shown in Figure 1. As can be seen, normal listeners perform well above chance ($p < 0.001$) at the smallest pitch changes of 6.25 and 12.5 cents, and perform at ceiling at all pitch distances including and above 25 cents.

-insert Figure 1 about here -

fMRI experiment

Stimuli

Stimuli consisted of seven pure-tone melodic patterns consisting of 21 tones each. All melodies had the same pitch contour starting at 1046 Hz (corresponding to the musical note C6) as shown in Figure 2, but was modified parametrically in terms of pitch distance between consecutive tones.

The stimuli were presented at one of the following seven pitch distances between tones (from smallest to largest): 0 (fixed pitch), 6.25, 12.5, 25, 50, 100, or 200 cents. The center value for all patterns was 1046 Hz. All tones were generated using MITSYN software (Henke, 1976). Each tone was 100 ms in duration, with 250 ms between each tone in the sequence, and the total duration of each sequence was 7350 ms.

-insert Figure 2 about here -

Task design

Subjects were scanned while passively listening to the stimuli as in the Zatorre and Belin (2001) study. Subjects heard the stimuli binaurally at a level of ~80 dB sound pressure level via Siemens MR-compatible pneumatic sound transmission headphones. Stimuli were presented in a pseudo-randomized order using Media Control Functions software (MCF, Digivox, Montreal, Canada). There were two runs, each with a total of 78 trials and two conditions: pitch (with 15 trials for the fixed pitch level, and 8 trials for each of the other six levels), and a baseline condition of silence (with 15 trials). Each run lasted about 15 minutes. A long inter-acquisition time of 10 seconds was used in order to minimize the noise-artifact from the scanner on the participants' ability to hear the stimuli. This also serves to avoid scanner noise contamination of the Blood oxygenation level-dependent (BOLD) response on the stimuli in the auditory cortices (Belin et al., 1999). Each acquisition lasted 2 seconds, and the stimuli were presented 0.4 seconds after each acquisition.

fMRI parameters and analysis

Scanning was performed on a Siemens (Erlangen, Germany) Vision 1.5 T MRI scanner at the Montreal Neurological Institute. A high resolution T1-weighted anatomical scan was obtained for anatomical localization for each subject [echo time (TE), 9.2 ms; repetition time (TR), 22 ms; matrix size, 256

x 256; voxel size, 1 x 1 x 1 mm], followed by two series of 78 T2* gradient echo-planar images. A headcoil was used to obtain 20 interleaved slices spanning the whole brain, and oriented along the Sylvian fissure (TE, 50 ms; TR, 10 s; matrix size, 64 x 64; voxel size, 5 x 5 x 5 mm).

In-house software (Collins et al., 1994) was used in the pre-processing of the BOLD images. The images were first spatially smoothed using a 12 mm full-width at half-maximum Gaussian blurring kernel, corrected for motion, and then were linearly transformed into standard stereotaxic space corresponding to the MNI/Talairach template (Collins et al., 1994). Next, statistical analysis based on a general linear model with correlated errors (Worsley et al., 2002) was performed on the BOLD data. Covariate analyses considering the BOLD response over all seven pitch distances were performed in order to investigate which brain areas showed activity that correlated in a linear fashion with increasing changes in pitch. Subtraction analyses, including four contrasts, were also performed in order to test for a non-linear relationship between BOLD activity and pitch distance. As a control contrast, all pitch conditions were summed and compared to silence. The fixed pitch condition was compared to silence to identify the brain areas responsive to fixed pitch information. In addition, a contrast of all pitch-variation conditions relative to fixed pitch was performed to identify the brain areas responsive to changing pitch information, while the largest pitch (200 cents) was compared to the fixed pitch (0 cents) condition to determine the regions responsive to the largest pitch change in particular.

A minimum threshold for statistical significance for the covariation and subtraction analyses was computed according to the random field theory, which corrects for the multiple comparisons involved in searching across a volume (Worsley et al., 2002). The results were deemed statistically significant at a *t*-threshold of 4.9 at $p < 0.05$, corrected for multiple comparisons across the whole-brain. Based on the results from the Zatorre

and Belin (2001) study, we expected that the auditory cortices would be specifically responsive to the pitch sequences. Thus, we used a region of interest (ROI) approach, which allows the use of a lower threshold value and hence greater sensitivity within a region defined *a priori*. For an ROI corresponding to the temporal neocortex with gray matter volume of roughly 17000 mm^3, the threshold applied was $t = 3.3$ at $p < 0.01$ (uncorrected).

Results

Imaging results

Covariation analyses

The covariation analysis considering the BOLD response across the seven pitch distances revealed activation in an area of secondary auditory cortex corresponding to the right planum temporale (PT; x = 64, y = -22, z = 4; t = 3.6). This region was lateral to the right primary auditory cortex, which is found in the medial portion of Heschl's gyrus (HG; Fig. 3A), and was determined with the aid of anatomical probability maps of HG (Penhune et al., 1996) and of PT (Westbury et al., 1999). There were no left auditory peaks in this analysis (Fig. 3A). Extraction of the % BOLD signal change (as compared to silence) for every pitch distance at this right PT peak revealed a significant positive linear trend ($p < 0.05$), where the BOLD signal increased as a function of increasing pitch distance (Fig. 3B; right side). The extraction of the BOLD signal at the analogous region in the left hemisphere did not reveal a significant linear trend (Fig. 3B; left side). However, it appeared that there was a nonlinear response such that BOLD signal increased only at 200 cents. This effect is explored further in the subtraction analyses (below).

In order to test whether there was a significant difference in the degree of change in the BOLD signal as a function of smaller pitch distances, we calculated the mean slope values of the BOLD data over all ten subjects at the left and right PT peaks for the first six conditions, and contrasted these

values across hemispheres. We excluded the largest pitch condition of 200 cents since both the right and left PT peaks showed a maximal BOLD response at this pitch distance. The average right PT slope was significantly greater than the left ($p < 0.01$, one-tailed t-test) (Fig. 3C), indicating that the right PT responds to a greater extent to smaller pitch distances, compared to the left PT, which on average has a near-zero slope over this range of pitch values.

-insert Figure 3 about here -

Subtraction analyses

As expected, the contrast of all sounds minus silence revealed significant bilateral activation centered around primary and nearby secondary auditory cortices (Fig. 4A), while the contrast of fixed-pitch minus silence revealed significant bilateral activation in only the medial portion of HG, likely within primary auditory cortex (Fig. 4B). Comparing the sum of all the pitch-change conditions (i.e., 6.25 through 200 cents) versus the fixed-pitch condition, revealed significant activation in only the right PT (x = 58, y = -22, z = 6; t = 5.9; Fig. 4C), in a location very comparable to that shown in the covariation analysis. Of greatest interest was the contrast of largest pitch distance (200 cents) minus fixed pitch (0 cents) because this contrast evaluates the presence of a non-linear response on the left side. It indeed revealed significant bilateral activation in both primary and secondary auditory areas including the PT and the superior temporal gyrus (STG) (Fig. 4D).

-insert Figure 4 about here –

Discussion

Relative functional asymmetry of the auditory cortex

We found that the right auditory cortex was preferentially responsive to small pitch changes as compared to the left. Both the covariation analyses and the

contrast of all pitch change conditions minus fixed pitch yielded significant activation specifically in the right PT, lateral to HG. As predicted, the right PT showed correlated changes in activity as a function of small pitch changes (i.e. less than 200 cents) (Fig 3). In contrast, the left PT was minimally sensitive to pitch changes less than 100 cents, but was responsive to the largest pitch distance of 200 cents as suggested by the ROI extraction (Fig 3B) and confirmed by the subtraction analyses (Fig 4D). Thus, our data provide support for the model of relative hemispheric asymmetry where the right auditory cortex has a higher resolution in the frequency domain compared to the left, as suggested in functional imaging studies (Schönwiesner et al., 2005; Zatorre et al., 2002). These results are also consistent with findings from a study that used intracerebrally recorded auditory evoked potentials in humans to demonstrate that neurons in the right auditory cortex were more sharply tuned to frequency as compared to those on the left (Liegeois-Chauvel et al., 2001).

This difference in frequency resolution between the hemispheres may account for why brain activation and pitch distance were linearly related in the right auditory cortex, but not the left. Regardless of this difference in resolution, increasing the consecutive pitch distance between tones in the melodic pattern results in a wider pitch range and spans a broader range of frequencies. An increasingly broad spectrum presumably activates a greater number of auditory neurons that are organized in a tonotopic fashion in both the left and right auditory cortices (Formisano et al. 2003; Talavage et al., 2004). Accordingly, one may expect a linear relationship between brain activation and pitch distance in both hemispheres. However, this linear trend is seen only in the right auditory cortex over small pitch distances, presumably because right auditory cortical neurons are more sharply tuned, and thus are more sensitive and show a greater BOLD response to the fine pitch changes, relative to the left auditory cortex. In contrast, we do not see this linear trend in the left auditory cortex since neural populations on that

side presumably have a coarser tuning function, and thus respond to larger pitch changes, but are only minimally responsive to small pitch changes.

The interpretation that the left auditory cortex does respond to pitch changes but only when they are relatively large is consistent with the idea that the hemispheric asymmetry is relative and not absolute. Support for this relative asymmetry comes from the study of patients with temporal-lobe excisions that encroached upon the right HG and secondary auditory cortex lateral to HG, similar to the region found here that was sensitive to pitch change (Johnsrude et al., 2000). These patients were able to judge the direction of pitch change between two tones, but had significantly elevated thresholds on this task, as compared to patients with more anterior right temporal excisions, sparing the lateral HG area, or to patients with left temporal excisions, and normal controls (Johnsrude et al., 2000). These authors suggested that this phenomenon could be explained by the idea that the patients with right lateral HG excisions could use their intact left auditory cortex to accomplish the task, but the less fine-grained representation of pitch in the left hemisphere would lead to a higher threshold (Johnsrude et al. 2000).

Hierarchical pitch processing in the auditory cortex

Although the prior studies (Johnsrude et al., 2000; Patterson et al., 2002; Schönwiesner et al., 2005; Zatorre and Belin, 2001) converge in implicating a network of right secondary auditory areas in the processing of spectral variations, the results across these studies do not correspond to exactly the same auditory regions. These differences are likely related to stimuli differences between experiments. For example, in contrast to the pure-tone melodic patterns used in the present study, in their fMRI study, Schönwiesner and colleagues (2005) employed novel noise-like stimuli that were perceptually unrelated to speech and music, but contained acoustic characteristics of both. When these stimuli were made more spectrally complex, brain activation was weighted to the right auditory cortex, with the

strongest asymmetry in an area of secondary auditory cortex at the border of the antero-lateral PT and STG, very similar to the right PT area found in our study. However, in contrast to the present study, both the right and left primary auditory cortices were sensitive to the spectral variations. This trend may be accounted for by the fact that complex spectral stimuli as used by Schönwiesner et al. (2005), are known to produce more activation than pure tones in HG and bilaterally on the lateral supratemporal plane (Hall et al., 2002), and that the highest degree of spectral spacing used in that study ($1/16^{th}$ of a 6-octave bandwith) was much coarser than the small frequency changes used here.

The right PT activation found in our study is posterior (by about 20 mm) to the anterior superior temporal area that was found to be responsive to spectral changes in the Zatorre and Belin (2001) study. In this case, both studies employed pure-tone, sequential, melodic stimuli, but the spectral stimuli used in the Zatorre and Belin (2001) study consisted of a random pure-tone sequence spanning a constant spectral range of one octave, whereas in our study, the pitch patterns all had the same melodic contour but varied in spectral range. Thus, the more posterior activation found here, may reflect that the processing of a fixed melodic contour involves more postero-lateral secondary auditory areas, whereas a random melodic contour favors more antero-lateral secondary auditory areas. Nonetheless, the present result is consistent with the findings that the hemispheric asymmetry in spectral processing is most apparent in regions beyond the primary auditory cortex.

Converging evidence for the importance of lateral belt cortex to pitch processing also comes from recent neurophysiological findings in the marmoset (Bendor and Wang, 2005). This study reveals the existence of pitch-sensitive neurons that respond with a consistent firing pattern to a variety of complex sounds that perceptually correspond to a given pitch. The

region identified, in belt cortex near the antero-lateral border of the primary cortex, is compatible with our findings here.

Both functional (Patterson et al., 2002) and anatomical (Hackett et al., 2001) findings indicate a hierarchy of pitch processing, where the center of activity moves antero-laterally away from the primary auditory cortex, with more complex pitch pattern processing. For example, in a recent fMRI study that sought to identify the main stages of melody processing in the auditory pathway, spectrally matched sounds that produce no pitch, fixed pitch, and melodies were all found to activate HG and PT, while more complex melodies activated regions beyond these areas including the STG and planum polare (Patterson et al., 2002). Consistent with this notion of hierarchical pitch processing, in the present study the processing of fixed pitch implicated primary auditory cortex bilaterally, while the processing of changing pitch patterns implicated secondary auditory areas as well, including the PT and STG, and with a right-weighted lateralization.

Conclusion

The present data provide further evidence for the presence of a network of right secondary auditory areas that are preferentially involved in the processing of sequential pitch information. The results are consistent with the model of relative hemispheric specialization and provide direct evidence that the secondary auditory cortices in the two hemispheres differ in their spectral resolution.

References

Belin P, Zatorre RJ, Hoge R, Evans AC, Pike B (1999) Event-related fMRI of the auditory cortex. Neuroimage 10:417-429.

Belin P, Zilbovicius M, Crozier S, Thivard L, Fontaine A, Masure MC, Samson Y (1998) Lateralization of speech and auditory temporal processing. J Cogn Neurosci 10:536-540.

Bendor D, Wang X (2005) The neuronal representation of pitch in primate auditory cortex. Nature 436:1161-1165.

Boemio A, Fromm S, Braun A, Poeppel D (2005) Hierarchical and asymmetric temporal sensitivity in human auditory cortices. Nat Neurosci 8:389-395.

Brechmann A, Scheich H (2005) Hemispheric shifts of sound representation in auditory cortex with conceptual listening. Cereb Cortex 15:578-587.

Collins DL, Neelin P, Peters TM, Evans AC (1994) Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. J Comput Assist Tomogr 18:192-205.

Formisano, E., Kim, D.-S., Di Salle, F., van de Moortele, P.-F., Ugurbil, K., and Goebel, R. (2003). Mirror-Symmetric Tonotopic Maps in Human Primary Auditory Cortex. Neuron *40*, 859-869.

Hackett TA, Preuss TM, Kaas JH (2001) Architectonic identification of the core region in auditory cortex of macaques, chimpanzees, and humans. J Comp Neurol 441:197-222.

Hall DA, Johnsrude IS, Haggard MP, Palmer AR, Akeroyd MA, Summerfield AQ (2002) Spectral and temporal processing in human auditory cortex. Cereb Cortex 12:140-149.

Halpern AR, Zatorre RJ (1999) When that tune runs through your head: a PET investigation of auditory imagery for familiar melodies. Cereb Cortex 9:697-704.

Henke WL (1976) An interactive dialogue language for time signal processing.
Cambridge, MA: MIT Research Laboratory of Electronics.

Hyde KL, Peretz I (2004) Brains that are out of tune but in time. Psychol Sci 15:356-360.

Johnsrude IS, Penhune VB, Zatorre RJ (2000) Functional specificity in the right human auditory cortex for perceiving pitch direction. Brain 123 (Pt 1):155-163.

Liegeois-Chauvel C, Giraud K, Badier JM, Marquis P, Chauvel P (2001) Intracerebral evoked potentials in pitch perception reveal a functional asymmetry of the human auditory cortex. Ann N Y Acad Sci 930:117-132.

Milner BA (1962) Laterality effects in audition. In: Interhemispheric relations and cerebral dominance (Mountcastle V, ed.), pp177–195. Baltimore, MD: Johns Hopkins University Press.

Patterson RD, Uppenkamp S, Johnsrude IS, Griffiths TD (2002) The processing of temporal pitch and melody information in auditory cortex. Neuron 36:767-776.

Penhune VB, Zatorre RJ, MacDonald JD, Evans AC (1996) Interhemispheric anatomical differences in human primary auditory cortex: probabilistic mapping and volume measurement from magnetic resonance scans. Cereb Cortex 6:661-672.

Peretz I (1990) Processing of local and global musical information by unilateral brain-damaged patients. Brain 113 (Pt 4):1185-1205.

Perry DW, Zatorre RJ, Petrides M, Alivisatos B, Meyer E, Evans AC (1999) Localization of cerebral activity during simple singing. Neuroreport 10:3979-3984.

Phillips DP, Farmer ME (1990) Acquired word deafness, and the temporal grain of sound representation in the primary auditory cortex. Behav Brain Res 40:85-94.

Poeppel D (2003) The analysis of speech in different temporal integration windows: cerebral lateralization as 'asymmetric sampling in time'. Speech Communication 41:245-255.

Robin DA, Tranel D, Damasio H (1990) Auditory perception of temporal and spectral events in patients with focal left and right cerebral lesions. Brain Lang 39: 539–555.

Schönwiesner M, Rubsamen R, von Cramon DY (2005) Hemispheric asymmetry for spectral and temporal processing in the human antero-lateral auditory belt cortex. Eur J Neurosci 22:1521-1528.

Scott, S.K., Wise, R.J.S. (2004) The functional neuroanatomy of prelexical processing in speech perception. Cognition 92: 13-45.

Talavage TM, Sereno MI, Melcher JR, Ledden PJ, Rosen BR, Dale AM (2004) Tonotopic organization in human auditory cortex revealed by progressions of frequency sensitivity. J Neurophysiol 91:1282-1296.

Warrier CM, Zatorre RJ (2004) Right temporal cortex is critical for utilization of melodic contextual cues in a pitch constancy task. Brain 127:1616-1625.

Westbury CF, Zatorre RJ, Evans AC (1999) Quantifying variability in the planum temporale: a probability map. Cereb Cortex 9:392-405.

Worsley KJ, Liao CH, Aston J, Petre V, Duncan GH, Morales F, Evans AC (2002) A general statistical analysis for fMRI data. Neuroimage 15:1-15.

Zatorre RJ (1988) Pitch perception of complex tones and human temporal-lobe function. J Acoust Soc Am 84:566-572.

Zatorre RJ, Belin P (2001) Spectral and temporal processing in human auditory cortex. Cereb Cortex 11:946-953.

Zatorre RJ, Belin P, Penhune VB (2002) Structure and function of auditory cortex: music and speech. Trends Cogn Sci 6:37-46.

Zatorre RJ, Evans AC, Meyer E (1994) Neural mechanisms underlying melodic perception and memory for pitch. J Neurosci 14:1908-1919.

Figure legends:

Figure 1: Pitch discrimination behavioral task results.
Performance of n=10 subjects expressed as mean percentage of hits (i.e. a "yes" response when there was a change) minus false alarms (F.A.; i.e. a "yes" response when there was no change) as a function of pitch change. Error bars represent standard errors.

Figure 2: Schematic of a melodic pattern used in the fMRI study.
Each black square corresponds to one tone, and the pitch distance between consecutive tones (P) in cents is shown along the vertical axis from a center pitch of 1046 Hz corresponding to the musical note C6.

Figure 3: fMRI results: covariation analyses.
A, Group (n=10) t-statistical map for the covariation analysis superimposed on the group average anatomical MRI. The right side of the brain image corresponds to the right side of the brain. Horizontal and coronal sections are shown on the left and right of the figure, respectively; the yellow arrows point to the right PT peak activation. *B*, Correlations of % BOLD signal change as a function of increasing pitch distance at the left and right PT. A trend line is drawn to demonstrate the significant ($*p < 0.05$) positive linear trend at the right PT, along with the corresponding Pearson *r* value. *C*, Average slopes of the %BOLD signal at the left and right PT. The ** indicates a significant result at $p < 0.01$ (one-tailed *t*-test).

Figure 4: fMRI results: subtraction analyses.
A, B, C, and D, Group (n=10) t-statistical maps for the four different contrasts, each of which are superimposed on the group average anatomical MRI. Images are shown as horizontal sections.

Figure 1:

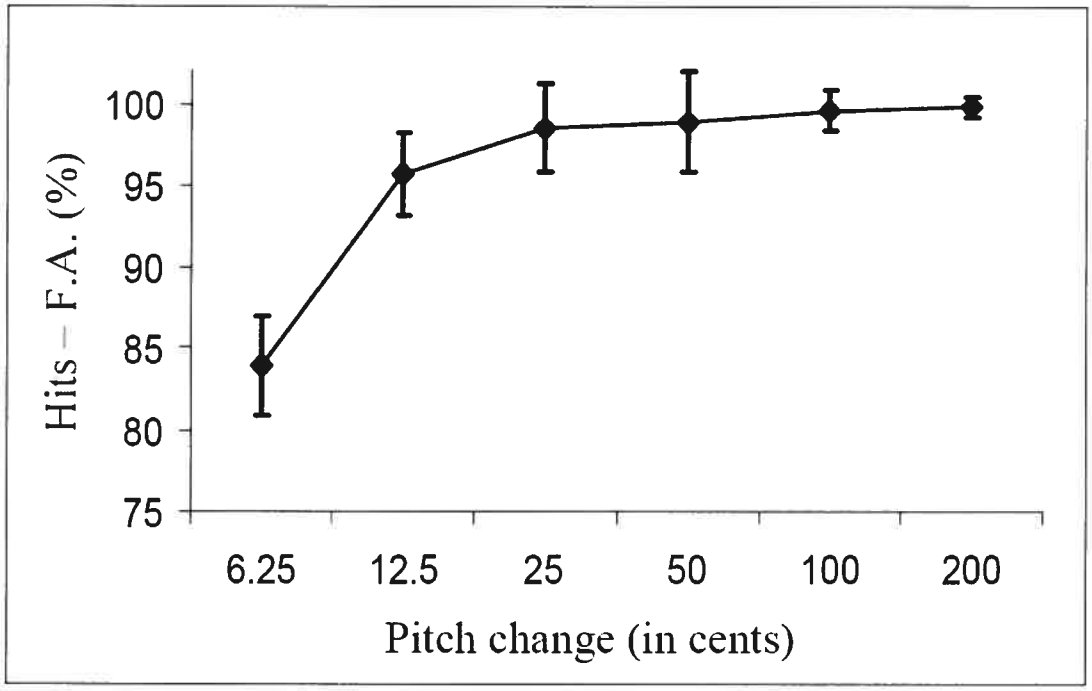

100
95
90
85
80
75
Hits – F.A. (%)
6.25
12.5
25
50
100
200
Pitch change (in cents)

Figure 2:

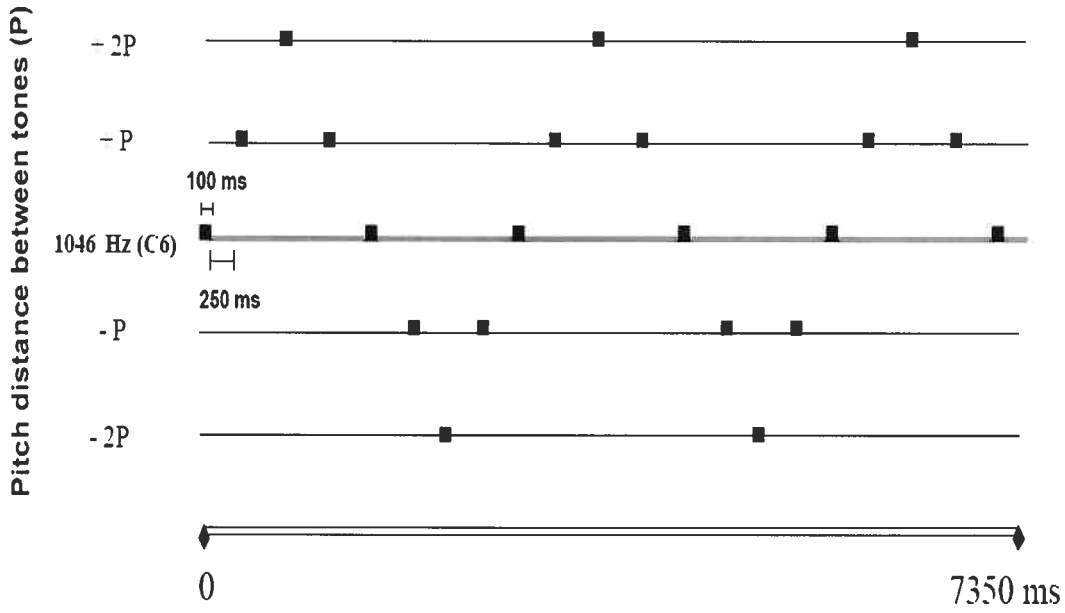

Pitch distance between tones (P)
- 2P
- P
100 ms
1046 Hz (C6)
250 ms
- P
- 2P
0
7350 ms

Figure 3:

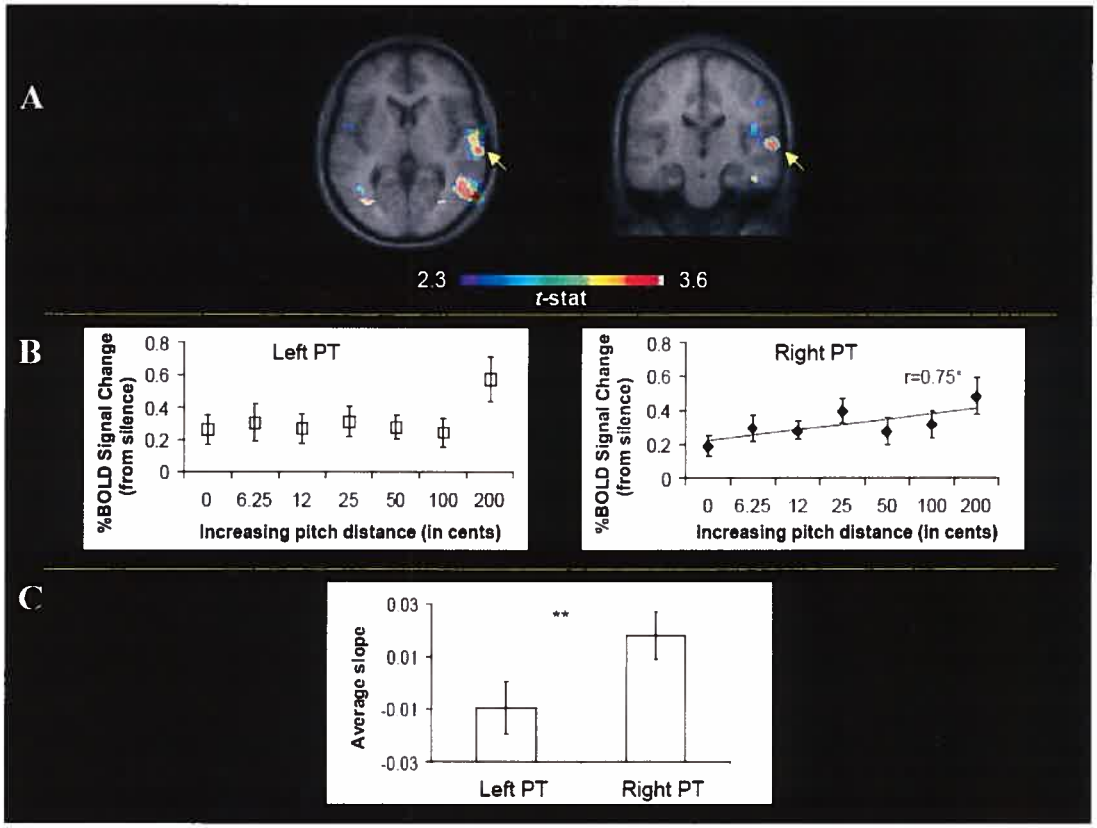
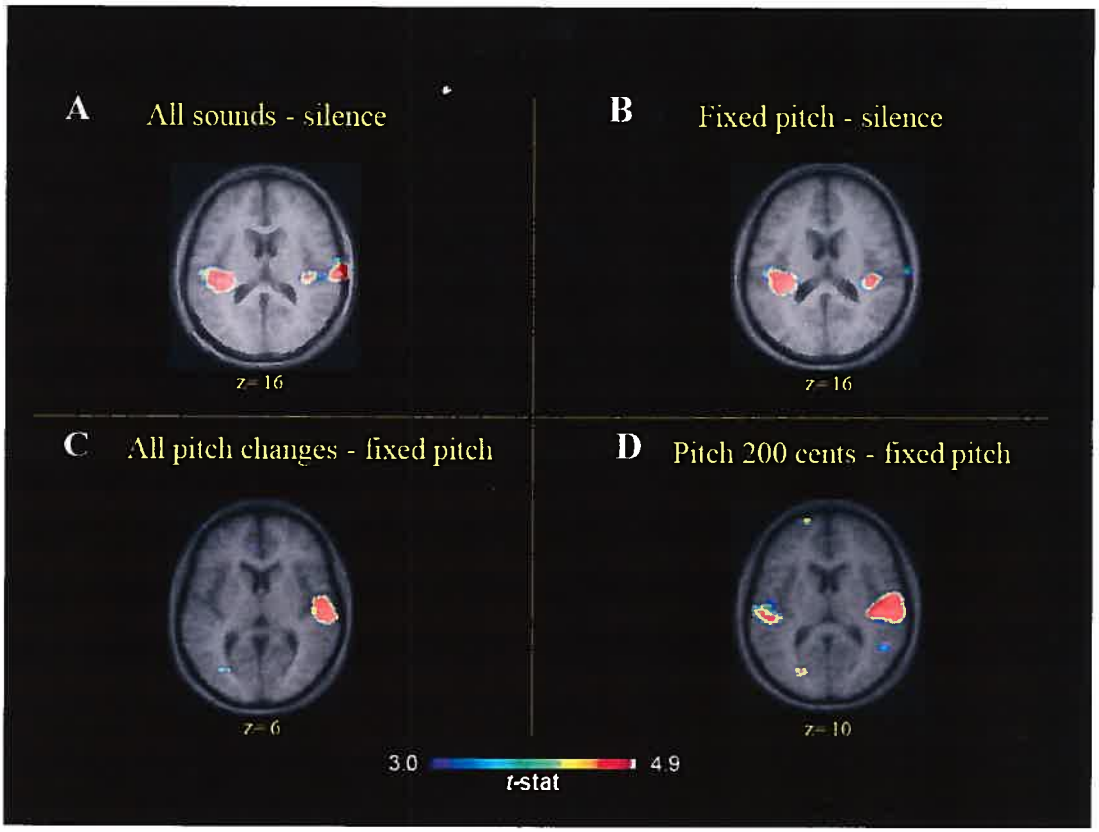

A
2.3
3.6
t-stat
B
Left PT
%BOLD Signal Change (from silence)
0.8
0.6
0.4
0.2
0
0 6.25 12 25 50 100 200
Increasing pitch distance (in cents)
Right PT
r=0.75*
%BOLD Signal Change (from silence)
0.8
0.6
0.4
0.2
0
0 6.25 12 25 50 100 200
Increasing pitch distance (in cents)
C
Average slope
0.03
0.01
-0.01
-0.03
**
Left PT
Right PT

Figure 4:


A
All sounds - silence
z= 16
B
Fixed pitch - silence
z= 16
C
All pitch changes - fixed pitch
z= 6
D
Pitch 200 cents - fixed pitch
z= 10
3.0
4.9
t-stat

THIRD ARTICLE:
PITCH AND TIME DISCRIMINATION IN CONGENITAL AMUSIA: BEHAVIORAL AND NEURAL CORRELATES

Pitch and Time Discrimination in Congenital Amusia:

Behavioral and Neural Correlates

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Abstract

Congenital amusia (or tone-deafness) is a lifelong disability that prevents otherwise normal functioning individuals from developing basic musical skills. While behavioral evidence indicates that it may be due to a deficit in pitch processing, there is little known about the neural correlates of this disorder. Here, functional magnetic resonance imaging (fMRI) was used to investigate the neural bases of pitch and time discrimination in a group of congenital amusic adults and musically-intact controls. Subjects listened passively to pure-tone melodic pitch patterns that were parametrically modified either in pitch distance, or in terms of temporal rate of presentation. Contrary to expectation, amusics exhibited a similar pattern of blood oxygenation level-dependent (BOLD) activation as controls in processing the melodies, and a deviant pattern of activation in processing the same melodies when they were presented at various temporal rates. These imaging results suggested that amusics have problems to capture pitch changes when they are presented rapidly. In order to verify this hypothesis, subjects were then tested in a behavioral paradigm where they were required to judge the direction of pitch change, or discriminate a pitch change, between two tones, when these were presented at various temporal rates. Amusics were unable to judge the direction of pitch change at even the slowest temporal rate, and had great difficulty relative to controls to discriminate the pitch changes at faster temporal rates. These results point to a complex deficit, involving pitch distance, pitch direction, and temporal resolution that may contribute to the musical impairments observed in congenital amusia.

Keywords: congenital amusia, tone-deafness, pitch and time processing, fMRI, behavioral and neural correlates

Introduction

Human societies have always produced and enjoyed music, but about four percent of the general population is not able to do so (Kalmus and Fry, 1980). The existence of a developmental disorder of musical abilities, colloquially known as 'tone-deafness', has been entertained for over one century (Grant-Allen, 1878; Geschwind, 1984). However, it is only recently that a large research effort has been made to study the origins of such a disorder, currently termed 'congenital amusia' (Peretz et al., 2001). This disorder is characterized by a severe life-long impairment in both the perception and production of music, that prevents otherwise normal functioning individuals from developing basic musical skills. While several studies have explored the behavioral manifestations of this disorder (Ayotte et al., 2002; Peretz et al., 2002; Hyde and Peretz, 2004; Foxton et al., 2004), there is little known about its neural correlates. The main objective of the present study was to further elucidate the neural bases of congenital amusia in terms of pitch and time discrimination.

Behavioral evidence suggests that congenital amusia is principally due to a deficit in the processing of pitch information, while temporal processing appears to be less affected. Most notably, every amusic individual tested to date has shown a severe problem in the detection of anomalous pitches inserted in popular melodies (Ayotte et al., 2002; Hyde and Peretz, 2005). The pitch anomalies consist of tones that do not belong to the key in which the melody has been written, and hence sound incongruous for listeners of Western music. Even young listeners with no formal musical training are sensitive to these key violations (Trainor and Trehub, 1994). In contrast, the amusics do not demonstrate such a clear-cut deficit in the time domain. For example, amusics appear to be able to detect a rhythmic deviation in the context of a single short melody (Hyde and Peretz, 2005), while about half of the amusics have been shown to have problems to discriminate a similar

rhythmic deviation between two melodies (Peretz et al., 2003). The discrepancy between these results is likely due to the fact that the latter discrimination task is more demanding relative to the first in terms of memory load. Thus, there seems to be a subset of amusics that are spared in some aspects of musical time processing, and a proportion that are impaired. In comparison, all amusic individuals seem to be impaired in terms of musical (tonal) pitch.

The presence of such a musical pitch deficit is supported at a neural level by findings from a recent voxel-based morphometry (VBM) study that explored for structural brain differences in amusics relative to musically-intact controls (Hyde et al., 2005). VBM is a computerized procedure that searches throughout the whole brain for differences in local concentration of brain tissue between groups (Ashburner and Friston, 2000), and has been effective in revealing brain abnormalities in developmental disorders (e.g. Watkins et al., 2002; Vinckenbosch et al., 2005; Boddaert et al., 2004). In our study (Hyde et al., 2005), in two independent data samples, amusics were shown to have reduced white matter concentration in the right inferior frontal gyrus, and that this anatomical anomaly was related to a pitch-based musical task. Given that right frontal regions have been shown to be central to the encoding of musical pitch (Koelsch et al., 2002; Tillmann et al., 2003), and that we know amusics are critically impaired in this regard (Ayotte et al., 2002; Hyde and Peretz, 2005), we inferred that this right frontal anomaly was one neural marker of the amusics musical pitch deficit.

This deficit might arise from a more elemental problem. A problem in fine-grained pitch discrimination may prevent the normal internalization of musical scales that have steps between consecutive notes of 1 or 2 semitones (corresponding to 1 or 2 adjacent keys on a keyboard). Most Western melodies (Vos and Troost, 1989), and those from other cultures (Dowling and Harwood, 1986) are constructed with such small pitch distances. Thus,

individuals who are unable to detect such small pitch changes, will miss an essential part of musical structure. The presence of a fine-grained pitch discrimination deficit has been confirmed in each amusic subject tested so far (Hyde and Peretz, 2004; Foxton et al., 2004). For example, amusics were impaired in detecting a small pitch deviation in a five-tone monotonic and isochronous sequence as compared to musically-intact controls (Hyde and Peretz, 2004). Their deficit was shown to be specific to the pitch domain since they performed as controls in detecting a slight time deviation in the same context (Hyde and Peretz, 2004). Amusics have also been shown to be impaired in judging the direction of pitch change between two tones (Foxton et al., 2004). Given that their pitch deficit included the critical semi-tone distance, we concluded that a severe and specific deficit in fine-grained pitch discrimination might well account for the musical impairments in congenital amusia.

To date, only one study has explored the neural basis of the pitch deficit in congenital amusia. In order to narrow down the neural locus of this fine-grained pitch deficit, Peretz et al. (2005) recently conducted an event-related potentials (ERPs) where congenital amusic individuals and musically-intact controls were required to detect a rare deviant tone in a sequence of repetitive standard tones while their ERPs were recorded. Amusics showed abnormal electrical brain responses to the pitch deviations in right-lateralized brain areas, and showed no brain response to pitch deviances smaller than one semitone, whereas controls did so consistently. In contrast, amusics showed an enlarged brain response to large pitch changes of 2 and 3 semitones, with an N2 (that was not present in controls) and a P3 almost twice as large as that observed in controls. These abnormal brain responses were inferred to be neural markers of the amusics' fine-grained pitch processing deficit. Given the limited spatial resolution of the ERP approach, it was not possible to localize the exact brain areas of these abnormal responses. However, the electrical activity of the auditory cortex of amusic

individuals appeared to be intact given that the N1 voltage distribution over the scalp is consistent with a localization of the generators in the secondary auditory cortex (Näätänen et al., 1987). These results converge with findings from the above VBM study (Hyde et al., 2005) showing that amusics appear to have a pitch-based neural anomaly that lies outside the auditory cortex.

These results were surprising since we expected to find a pitch-based neural anomaly in the right auditory cortex of amusics, given the role of this region in various aspects of musical pitch processing. For example, studies of brain-lesioned patients have shown that the right auditory cortex is critical for melody discrimination (Milner, 1962), in the perception of missing fundamental pitch (Zatorre, 1988), in the perception of melody in terms of its global contour (Peretz, 1990), in perceiving the direction of pitch change (Johnsrude et al., 2000), and in using melodic contextual cues in pitch judgments (Warrier and Zatorre, 2004). Evidence from neuroimaging studies of normal listeners is consistent with these findings, showing an asymmetry favoring right auditory regions in melodic processing (Zatorre et al., 1994; Patterson et al., 2002; Hyde et al., 2003), in the maintenance of pitch while singing (Perry et al., 1999), imagery for tunes (Halpern and Zatorre, 1999), and in the detection of deviant chords (Tervaniemi et al., 2000).

While pitch processing appears to favor the right hemisphere, time processing seems to be weighted to left auditory cortical structures. For example, findings from studies of brain-lesion patients (Phillips & Farmer 1990; Tallal et al, 1993; Ehrlé et al., 2001) single-unit-electrode recordings (Liégeois-Chauvel et al., 1999), auditory steady-state electrophysiological data (Yamasaki et al., 2005) and neuroimaging data (Belin et al., 1998; Zatorre and Belin, 2001; Schönwiesner et al., 2005), have shown that left auditory cortical regions play a critical role in rapid temporal processing. Zatorre and colleagues (2002) have recently proposed that the auditory system has developed two parallel and complementary systems, one in each hemisphere,

specialized for differential resolution in the spectral and temporal domains, as a need to optimally process incoming simultaneous spectral and temporal acoustic information from the environment. A similar proposition has been made by Poeppel and colleagues (2003) who suggested that different time integration windows characterize the left and right auditory cortices, with faster temporal information (i.e. 25–50 ms) processed in left auditory areas and slower information in the right (i.e. 200–300 ms). Support for the concept of relative hemispheric asymmetry comes from neuropsychological (Robin et al., 1990), electrophysiological (Liégeois-Chauvel et al., 2001) and neuroimaging studies (Zatorre and Belin, 2001; Boemio et al., 2005; Brechmann et al., 2005; Schönwiesner et al., 2005;). The Zatorre and Belin (2001) study is of particular importance since it serves as a model for the present study. With the aim to test the theory of relative hemispheric asymmetry, in this PET study, musically-intact subjects were scanned while passively listening to pure-tone sequences that varied either in terms of spectral complexity or temporal rate (Zatorre and Belin, 2001). As expected, the responses to the spectral features were weighted towards right auditory areas, whereas responses to the temporal features were weighted towards the left. These findings were interpreted as reflecting differential resolution in the spectral domains and temporal in right and left auditory cortices, respectively.

Here we employed functional magnetic resonance imaging (fMRI) to investigate the neural correlates of pitch and time discrimination in congenital amusia. It is possible that we were previously unable to detect a neural anomaly in the auditory cortex of amusic individuals due to the fact it may be too subtle to be captured by VBM or ERP techniques. In order to target a potential neural anomaly thought to exist in the auditory cortex of amusic individuals, here we used pitch sequences known to elicit responses in the auditory cortices (Zatorre and Belin, 2001; Hyde et al, 2003). Congenital amusic subjects and musically-intact controls were scanned while passively

listening to pure-tone melodic patterns that were parametrically modified either in pitch distance, or in terms of temporal rate of presentation. Given the amusics pitch deficit (Hyde and Peretz, 2004; Foxton et al., 2004), we hypothesized that they would show a deviant pattern of BOLD activation as compared to controls in discriminating the pitch changes, specifically in the right auditory cortex. Based on the behavioral evidence that amusics perform as musically-intact controls in time discrimination (Hyde and Peretz, 2004), we did not expect to find any particular difference in brain activation in amusics relative to controls along the temporal dimension.

To better understand these imaging results, we next conducted a second, behavioral study, where we tested the ability of amusics to detect varying pitch changes presented at various temporal rates. The pitch distances and temporal rates were the same as those used in the fMRI study, however this time, the subjects heard pairs of isolated tones (and not tone sequences) that were similar to those used in previous psychophysical testing (Johnsrude et al., 2000, Gougoux et al., 2004). As in these previous studies, following each tone pair, subjects either performed a pitch direction judgment, by deciding whether the final tone rose or fell, or a pitch detection judgement, by deciding if the two tones were the same or different. Although amusics have previously been shown to have problems in both pitch direction and detection judgements (Foxton et al., 2004; Hyde and Peretz, 2004), their ability to discriminate pitch changes as a function of temporal rate of presentation has not yet been evaluated. Based on evidence that normal listeners find it increasingly difficult to discriminate pitch changes between two tones when these are presented at increasingly rapid temporal rates (Hartmann et al., 1985; Gougoux et al., 2004), we predicted that amusics would show amplified difficulties relative to musically-intact controls to capture rapid changes in pitch.

Study 1: fMRI experiment

Materials and Methods

Subjects

Nine congenital amusic subjects and nine musically-intact controls, matched in age, education and handedness, participated in the fMRI experiment. All amusic subjects had been thoroughly evaluated on previous testing (Ayotte et al., 2002, Hyde and Peretz, 2004). All subjects had normal intellectual, memory and language skills, normal hearing with respect to their age, and none had any previous neurological or psychiatric history. Subject characteristics are presented in Table 1. All amusics were impaired relative to controls on the Montreal Battery of Evaluation of Amusia (MBEA), a battery of music perception tests used to diagnose congenital amusia (Peretz et al., 2003). The battery involves six tests, which test melodic and rhythmic discrimination as well as sense of meter and musical memory. The global MBEA scores (averaged over all six tests) for amusics and controls are summarized in Table 1. All amusic subjects were also impaired relative to controls in detecting a small pitch deviation in a five-tone monotonic and isochronous sequence, whereas they performed as controls in detecting a slight time deviation in the same context (Hyde and Peretz, 2004). The mean scores for the pitch and time discrimination tasks for amusics and controls are summarized in Table 1. All subjects gave informed written consent for a protocol approved by the Montreal Neurological Institute Ethics Review Board.

-insert Table 1 about here-

Stimuli

The stimuli consisted of fourteen pure-tone melodic patterns that were based on those used in the Zatorre and Belin (2001) study. A schematic of a melodic pattern is shown in Figure 1. Each black square corresponds to one tone, and the pitch distance between consecutive tones (P) is shown along the vertical axis. All melodies had the same pitch contour starting at 1046 Hz

(corresponding to the musical note C6), but was modified parametrically either in terms of pitch distance or in temporal rate. The stimuli for the pitch condition were presented at a constant temporal rate of tone duration 340 ms, at one of the following seven pitch distances between tones (from smallest to largest): 0 (fixed pitch), 6.25, 12.5, 25, 50, 100, or 200 cents (where 1 cent is a unit of equal log frequency separation; 1 octave = 1200 cents and 1 semitone = 100 cents). The center value for all patterns was 1046 Hz. The stimuli for the time condition were presented at a constant pitch distance between tones of 200 cents, at one of the following seven temporal rates with tone duration (from slowest to fastest): 1460, 730, 367, 183, 91, 45, 22 ms. Every sequence had a constant total duration of 7350 ms, with 10 ms between tones. All tones were generated using MITSYN software (Henke, 1976).

-insert Figure 1 about here -

Task design

Subjects were scanned while passively listening to the stimuli as in Zatorre and Belin (2001). Subjects heard the stimuli binaurally at a level of ~80 dB sound pressure level via Siemens MR-compatible pneumatic sound transmission headphones. Stimuli were presented in a pseudo-randomized order using Media Control Functions software (MCF, Digivox, Montreal, Canada). There were two runs, each with a total of 136 trials and three conditions: pitch (with 16 trials for the fixed pitch level, and 8 trials for each of the other six levels), time (with seven levels and eight trials per level), and a baseline condition of silence (with sixteen trials). Each run lasted 25 minutes. A long inter-acquisition time of 10 seconds was used in order to minimize the noise-artifact from the scanner on the participants' ability to hear the stimuli. This also serves to avoid scanner noise contamination of the BOLD response on the stimuli in the auditory cortices (Belin et al., 1999). Each acquisition

lasted 2 seconds, and the stimuli were presented 0.4 seconds after each one. A schematic of the scanning paradigm is shown in Figure 2.

-insert Figure 2 about here -

fMRI parameters and analysis

Scanning was performed on a Siemens (Erlangen, Germany) Vision 1.5 T MRI scanner at the Montreal Neurological Institute. A high resolution T1-weighted anatomical scan was obtained for anatomical localization for each subject [echo time (TE), 9.2 ms; repetition time (TR), 22 ms; matrix size, 256 x 256; voxel size, 1 x 1 x 1 mm], followed by two series of 136 T2* gradient echo-planar images. A headcoil was used to obtain 20 interleaved slices spanning the whole brain, and oriented along the Sylvian fissure (TE, 50 ms; TR, 10 s; matrix size, 64 x 64; voxel size, 5 x 5 x 5 mm).

In-house software (Collins et al., 1994) was used in the pre-processing of the BOLD images. The images were first spatially smoothed using a 12 mm full-width at half-maximum Gaussian blurring kernel, corrected for motion and then were linearly transformed into standard stereotaxic space corresponding to the MNI/Talairach template (Collins et al., 1994). Next, statistical analysis based on a general linear model with correlated errors (Worsley et al., 2002) was performed on the BOLD data. First, the stimulus conditions were set up in a design matrix corresponding to each acquisition. Second, the linear model was solved for, yielding the effects, standard deviations and t-statistics for each contrast, for each individual run. Next, the two runs for each subject were combined using these effects and standard deviations. These results were then combined yielding group statistical maps for the amusics (all 9 subjects) and the controls (all 9 subjects). Four *t* statistic subtraction images were generated for each group. As a control contrast, all pitch conditions were summed and compared to silence. The contrasts of all pitch-variation conditions relative to fixed pitch, and fastest temporal rate relative to fixed

pitch, were performed in order to isolate the brain areas responsive to changing pitch information, and temporally changing pitch information, respectively. The fastest temporal rate condition was compared to the slowest one so as to provide a more precise contrast of the brain areas implicated in the temporal dimension of rapidly changing pitch information. In addition, covariate analyses considering the BOLD response across the pitch distances and the temporal rates, respectively, were performed on these data within each group to investigate which brain areas showed activity that correlated in a linear fashion with increasing changes in pitch or temporal rate. Finally, the same subtraction and covariate analyses were performed between-groups to compare patterns of BOLD activity between amusics and controls.

A minimum threshold for statistical significance for the subtraction and covariation analyses was computed according to the random field theory, which corrects for the multiple comparisons involved in searching across a volume (Worsley et al., 2002). We first employed a whole-brain statistical threshold of $t = 5.0$ for the within-group, and $t = 4.7$ for the between-group analyses, both at $P < 0.05$ (corrected for multiple comparisons). In addition, we used a region of interest (ROI) approach since we expected to find differences in BOLD activity between groups specifically in the auditory cortices. An ROI including the primary auditory cortex (Heschl's gyrus: HG) and the planum temporale (PT) were defined bilaterally with the use of prior anatomical probability maps of these regions (Penhune et al., 1996; Westbury et al., 1999). The ROI had a volume of about 9401 mm^3 and the threshold of significance was $t = 3.5$ for the within-group, and $t = 3.4$ for the between-group analyses, each at $P < 0.05$ (corrected for multiple comparisons).

Results

Control contrast

In both the amusic and control groups, comparing all conditions relative to a

baseline of silence showed an increased BOLD response bilaterally in HG, and extensive bilateral activation of secondary auditory areas throughout the superior temporal gyri (STG) (Table 2). These results were present in the same areas in each individual subject, in each group.

-insert Table 2 about here -

Pitch results

The contrast of all pitch-variation conditions relative to fixed pitch revealed an increased BOLD response bilaterally in the PT in the control group (Table 2; Fig. 3 A, left side). For the same contrast, the amusic group showed similar results as controls (Table 2; Fig. 3 A, right side). There were no significant areas of BOLD decreases. The covariation analysis considering the BOLD response across all seven pitch distances, yielded bilateral activation of the PT in the control group (Table 2; Fig. 3 A, left side). Again, the amusic group showed similar results as controls (Table 2; Fig. 3 A, right side). The results from the subtraction and covariation analyses were present in the same areas in each individual subject, in each group.

In order to investigate the % BOLD signal change (as compared to silence) across all pitch distances, we extracted the BOLD signal at both the right and left PT peaks in each group. Controls showed a significant positive linear trend of increasing BOLD response with increasing pitch distance, at both peaks (Fig. 3 B, left side). Amusics showed the same trend in similar regions bilaterally (Fig. 3 B, right side). For both controls and amusics, there was no significant difference in the average slope of the BOLD signal change between the left and right peaks (Fig. 3 C).

Relative to controls, the amusics showed more extensive increased BOLD activation in anterior STG regions bilaterally, and in the right HG for the pitch

contrast and pitch covariation. However, this was not significant in the between-group analysis.

-insert Figure 3 about here -

Time results

For the contrast of fastest temporal rate relative to fixed pitch, the control group showed an increased BOLD response in bilateral auditory areas (including the left HG and the right PT), with a left-weighted lateralization (Table 2). The amusic group also showed bilateral activation of HG, but did not show the left-weighted asymmetry as controls (Table 2). For the contrast of fastest relative to slowest temporal rate, the control group showed an increased BOLD response bilaterally in HG, with a left-weighted asymmetry (Table 2; Fig. 4 A, left side). Again, the amusic group showed bilateral activation of HG, but not the left-weighted asymmetry as controls (Table 2; Fig. 4 A, right side). There were no significant areas of BOLD decreases. In the control group, a covariation analysis involving all temporal rates yielded bilateral activation principally in HG and some secondary auditory areas, with a left-weighted lateralization (Table 2; Fig. 4 A, left side). The amusic group also showed bilateral activation in the HG and secondary auditory areas, but did not show the same left-weighted lateralization as controls (Table 2; Fig. 4 A, right side). The results from the subtraction and covariation analyses were present in the same areas in each individual subject, in each group.

In order to investigate the % BOLD signal change (as compared to silence) across all temporal rates, we extracted the BOLD signal at both the left and right HG peaks in each group. Both controls and amusics showed a positive linear trend of increasing BOLD response with increasing temporal rate at both peaks (Fig. 4 B). However, only controls showed a stronger linear trend in the left HG as compared to the right HG. In addition, only the controls showed a larger average slope of the BOLD signal change in the left HG as

compared to the right HG, though this difference was not quite significant (Fig. 4 C, left side). In contrast, the amusic group did not show this left-weighted tendency (Fig. 4 C, right side).

-insert Figure 4 about here -

The between-group analysis for the contrast of fastest temporal rate minus fixed pitch confirmed the within-group findings in revealing that controls had a significantly stronger BOLD activation relative to amusics in the left HG (Fig. 5 A left). The contrast of fastest relative to slowest temporal rate yielded consistent findings, though slightly below the ROI significance threshold (Fig. 5 A middle). The between-group analysis for the time covariation also confirmed the within-group findings, in revealing that controls had a stronger linear trend of the BOLD signal over all temporal rates relative to amusics in the left HG, though slightly below the ROI significance threshold (Fig. 5 A). Moreover, a significant difference emerged when comparing the average slope of the BOLD signal data between groups for the left HG peak, but not for the right HG peak (Fig. 5 B).

-insert Figure 5 about here –

Discussion

As expected, controls showed bilateral activation of the PT in processing the pitch variations. These results are consistent with recent neuroimaging findings of bilateral PT activation in the processing of sound stimuli containing regular spectrotemporal modulations (Langers et al., 2003) and in the analysis of sequences of pitch and acoustic spatial locations (Warren and Griffiths, 2003). However, we expected to find a right-hemisphere asymmetry of auditory activation based on more similar studies of pitch processing, where the right auditory cortex was preferentially involved

in processing pitch variations in similar melodic tonal sequences (Zatorre and Belin, 2001; Hyde et al., 2003), or noise-like stimuli (Patterson et al., 2002; Schönwiesner et al., 2005). Moreover, in the present study, both the left and right PT were more responsive with increasing pitch distance within the melodic sequence. This linear trend may be explained by the idea that increasing the pitch distance results in a broader spectrum, which in turn activates a greater number of auditory neurons that are organized in a tonotopic fashion in both the left and right auditory cortices (Formisano et al. 2003; Talavage et al., 2004), and thus lends to a stronger BOLD signal. However, we expected this linear trend to be stronger in the right hemisphere relative to the left, based on findings from a recent fMRI study from our laboratory that investigated pitch pattern perception in musically-intact listeners using similar melodies as used here (Hyde et al., 2003). In the Hyde et al., 2003 study, the BOLD signal increased as a function of increasing pitch distance specifically in the right PT, but not on the left. We interpreted these results as being due to the fact that right auditory cortical neurons are sharply tuned, and thus respond to the fine pitch changes, whereas neural populations on the left side have a coarser tuning function, and thus respond to larger pitch changes, but are minimally sensitive to small pitch changes (Liegeois et al., 2001; Hyde et al., 2003).

The finding that controls did not show the same right auditory asymmetry in response to the pitch changes as found in the Hyde et al., 2003 study, may be explained by the fact that the controls tested here (age range: 46-62 years) were significantly older ($P < 0.001$) relative to the University students tested in the Hyde et al., 2003 study (age range: 21-36 years), and that older adults typically exhibit reduced cortical asymmetry (Carbeza 2002, 2004). It has been suggested that older adults counteract age-related neural decline through a functional compensation process, whereby, with diminished activity of the principal hemisphere, the opposite hemisphere becomes responsive, and thus results in a reduced cortical asymmetry (Carbeza 2002, 2004). Age-

related asymmetry reductions have been principally demonstrated in the prefrontal cortex in memory tasks (Carbeza 2004), but also in temporal and parietal brain regions, as evidenced by functional neuroimaging studies of face encoding (Grady et al., 2000; 2002), and inhibitory control (Nielson et al., 2002). Thus, it is possible that in the present study, a neuroplastic reorganization occurred whereby, with diminished activity of the right PT in response to the pitch variations, there was an increased involvement of the left PT, resulting in a more bilateral pattern of auditory brain activation.

Given the evidence that congenital amusia is principally a pitch-based disorder (Hyde and Peretz, 2004; 2005), it was surprising to see that amusics showed a similar pattern of bilateral auditory activation as controls in processing the changing pitch sequences. However, these results are consistent with the findings from the VBM (Hyde et al., 2005) and ERP studies (Peretz et al., 2005) of the amusic brain, which did not reveal any neural anomaly in the auditory cortices of amusics. It is possible that there is a subtle difference in auditory cortical regions in the amusic brain that we have not been able to detect with these techniques. The present fMRI data, along with the VBM and ERP studies, suggest that the most salient pitch-based neural anomaly in the amusic brain lies outside the auditory cortex.

Most of the research into congenital amusia to date has been concentrated on pitch processing, given that the condition has been found to primarily be a pitch-based deficit. Consequently, there has been less focus on the temporal aspects of this condition. To our knowledge, no study has specifically investigated how amusic individuals process temporally changing pitch information. In the present study, amusics showed bilateral activation as musically-intact controls, principally in the primary auditory cortex, in response to changing pitch information when presented at various temporal rates. Moreover, these regions were more responsive with increasing temporal rate. However, while activation was weighted to the left auditory

cortex in controls, the amusics did not show this left-hemisphere asymmetry. These fMRI data revealed that amusics do not have the same specialization of the left auditory cortex for rapid temporal processing as found in normal listeners (Zatorre and Belin, 2001; Schönwiesner et al, 2005). These imaging data suggest that amusics do not process temporally changing pitch information in the same way as controls. We hypothesized that this difference in brain activation was a neural marker reflecting that amusics may have problems to capture fine pitch changes when they are presented rapidly. We discuss this idea in detail in the general discussion (following study 2).

Study 2: Behavioral experiment

Materials and Methods

Subjects

Six of the nine amusic subjects, and seven of the nine controls that participated in the fMRI study, were tested in the behavioral experiment. The remaining subjects were not available for testing.

Stimuli

Stimuli were fifteen different isolated pure-tone pairs that were parametrically modified in terms of pitch distance between tones and temporal rate, as in the fMRI study. There were three different tone pairs corresponding to three pitch distances between tones (from smallest to largest): 50, 100, and 200 cents. On half of the trials the pitch changes were presented in the ascending direction, and on the other half, descending. Each of these tone pairs was presented at each of five temporal rates with tone duration (from slowest to fastest): 367, 183, 91, 45, 22 ms. The tone pairs were presented sixteen times each, for a total of 240 trials. All tones were generated using MITSYN software (Henke, 1976).

Procedure

All subjects were tested with the same stimuli, in two separate conditions. In a *direction* condition, subjects had to decide whether the final pitch of the tone pair went 'up' or 'down'. In a *discrimination* condition, subjects had to decide whether the two tones were the 'same' or 'different'. In both conditions, subjects responded by a button press, left for 'up' or 'different' and right for 'down' or 'same'. The order of conditions was counterbalanced across subjects and each condition lasted about 15 minutes. Stimuli were presented in a random order via Media Control Functions (MCF, Digivox, Montreal, Canada). Subjects heard stimuli binaurally through headphones at a level of ~80 dB sound pressure level.

Results

In the direction condition, controls performed better at larger pitch distances, and increasingly better with slower temporal rates (Fig. 6 A). In contrast, amusics performed at chance when computing the average score over all temporal rates at each of the three pitch distances: at 50 cents [t (5) = 1.43, P = 0.21], 100 cents [t (5) = 1.94, P = 0.11], and 200 cents [t (5) = 2.29, P = 0.07] (Fig. 6 A).

In the discrimination condition, controls again performed better at larger pitch distances, and increasingly better with slower temporal rates (Fig. 6 B). While amusics showed this same trend as controls, overall, they do not perform as well (Fig. 6 B). A 2 (groups) by 3 (pitch distance) by 5 (temporal rate) repeated measures analysis of variance (ANOVA) revealed that controls performed better than amusics overall with a significant group effect [F (1, 11) = 8.8, $P < 0.05$]. While there were no significant interactions involving pitch distance, there was a significant interaction between temporal rate and group [F (4, 44) = 7.5, $P < 0.001$]. This is explained by the fact that controls perform better than amusics over all three pitch distances, at all temporal rates, except for at the slowest temporal rate of 367 ms. Amusics match control

performance at this rate, at all pitch distances: at 50 cents (t (11) = 1.09, P = 0.30), 100 cents (t (11) = 0.14, P = 0.89), and 200 cents (t (11) = 0.81, P = 0.43). Given that the sample sizes were relatively small, non-parametric Mann–Whitney U tests were also performed on these data, and yielded the same pattern of results.

-insert Figure 6 about here –

Discussion

The chance performance of amusics on the pitch direction task is in contrast to that of controls who perform as expected from findings in normals in a similar task (Gougoux et al., 2004). The amusics' poor performance on this pitch direction task is consistent with previous psychophysical findings (Foxton et al., 2004) that they have a severe deficit in pitch direction judgments. In the pitch discrimination task, amusics perform worse than controls, except at the slowest temporal rate of 367 ms, where they match control performance. Task difficulty is not an issue since amusics could detect even fine pitch changes (50 cents) as controls at this temporal rate. This finding was unexpected given that amusics have previously been shown to have problems to discriminate pitch changes of 50 cents (Hyde and Peretz, 2004). However, in contrast to the tone-pairs used here, Hyde and Peretz (2004) employed a five-tone sequence. Thus, it is possible that amusics find it easier to discriminate fine pitch distances (i.e. 50 cents) in the context of tone pairs. In addition, the tempo used here of 367 ms is slightly longer than the tempo used in Hyde and Peretz (2004) of 350 ms, which may facilitate the pitch judgment.

The finding that amusics match control performance at the particular temporal rate of 367 ms is key since this suggests that amusics are impaired relative to controls when pitch changes are presented rapidly, up to a certain tone duration threshold. Over roughly 80% of Western music has a tempo within

the range of 370 – 740 ms per note (Moleants et al., 2002, 2003). This tempo range is also consistent with the pioneer work of Fraisse on preferred tempo in music (Fraisse, 1982). However, pitch changes in a musical context can often range from 150 – 1000 ms per note (Warren et al., 1991). The present data show that amusic individuals have problems to perceive even evident pitch changes (i.e. at 200 cents) at temporal rates that can be musically-relevant. Thus, we suggest that the deficit seen here may contribute in part to the amusics musical problems.

In the stimuli used here, the pitch change and temporal rate within each melodic pattern were constant. However, in a true musical context, both pitch and temporal information fluctuate over time. Thus, one may expect that amusics would have even greater problems to discriminate similar pitch changes in a musical context. Support for this idea comes from findings that a majority of amusics have problems to synchronize with a musical beat (Dalla Bella and Peretz, 2003), and that a proportion of amusics were impaired in the discrimination of a rhythmic change in terms of temporal groups between two melodies (Peretz et al., 2003). However, more recent findings have shown that amusics were spared in the ability to detect a slight rhythmic break (or pause) in a melody (Hyde and Peretz, 2005). These findings reflect that a subset of amusics are impaired in certain aspects of musical rhythmic processing, and a subset are spared. Nonetheless, the present behavioral results showed that every amusic subject had problems to discriminate pitch changes when they were presented rapidly. We offer possible explanations to account for the amusics' temporal pitch deficit in the following section.

General discussion:

One way to explain the temporal pitch deficit seen here in amusics is to consider that pitch and time are processed by independent systems.

Evidence in favor of this notion comes from lesion studies of cases of impaired pitch but intact rhythmic processing (e.g. Peretz, 1990; Piccirilli et al., 2000, Murayama et al., 2004), as well as the reverse case of impaired rhythmic but spared pitch processing (e.g. Brust, 1980; Mavlov, 1980; Di Pietro et al., 2004). Further support comes from the theory of relative hemispheric specialization where the auditory system developed two independent but complementary systems - one in each hemisphere - where right auditory cortical structures appear to be specialized for spectral processing, and left auditory regions for rapid temporal processing (Zatorre et al., 2002). If it is assumed that there is a fixed amount of cognitive and neural resources available for general auditory processing, and that enhanced processing of one domain (whether pitch or time) will come at a cost to the other, it is plausible to expect a relative trade-off in terms of the allocation of resources for both pitch and time processing. For example, if the temporal parameter becomes more demanding (in this case, in terms of increased temporal rate), then this will necessarily diminish the amount of resources remaining for accurate pitch processing. Such a shift in resource allocation may explain why the musically-intact individuals in our study, and other studies (Hartmann et al., 1985; Gougoux et al., 2004), had difficulty to detect even obvious pitch changes (i.e. at 200 cents) when they are presented at faster speeds. In the case of amusic individuals, this deficit is greatly amplified relative to normal listeners, most likely due to the fact that amusics have a pre-existing impaired pitch processing system, even prior to adding temporal complexity.

The hypothesis of a shift in resource allocation seems plausible to account for the amusics temporal pitch deficit, however, the concept of a 'resource' remains unspecified. Moreover, in contrast to the view that pitch and time are processed independently, other evidence shows that both dimensions are processed by common neural mechanisms. For example, both left and right-brain-damaged patients have shown simultaneous melodic and temporal

deficits (Schuppert et al., 2000), and recent PET data in normal listeners revealed similar patterns of bilateral activation in the processing of pitch and duration patterns (Griffiths et al., 1999). Peretz and Kolinsky (1993) offered a concensus to this issue by proposing that melody and rhythm are processed independently up to a certain point, after which there is an integration of these two dimensions at a unified stage of processing. This theory serves well to interpret the present results. From this perspective, it is possible that the amusics severe deficit in the pitch domain would cause a disturbance in the system that integrates pitch and time information, and subsequently compromise normal temporal processing. Thus, as we have previously suggested (Peretz and Hyde, 2003; Hyde and Peretz, 2004), amusics would not be able to apply normal specialized fine temporal analysis as a cascade effect of their deficits in both pitch distance and direction. The idea that pitch distance, direction and rhythmic information may be processed within an integrated system at some level, and thus necessarily interact, is supported by findings that tempo judgments of melodies are influenced by variations in terms of pitch distance, pitch direction, and rhythmic accent structure (Boltz, 1998). This helps to explain why amusics have no problem to discriminate slight temporal changes in an isochronous and monotonic tone sequence (Hyde and Peretz, 2004), but are unable to discriminate changes in pitch when stimuli vary in terms of pitch distance, direction and time changes, as in the present study.

Interestingly, the amusics' deficit in processing rapidly changing pitch information seen here appears to be limited to the musical domain, since previous findings have shown that amusics are spared in processing pitch changes in speech (Ayotte et al., 2002). This is counter-intuitive given that rapid temporally processing is key in speech perception (see Zatorre et al., 2002 for a review). However, pitch variations in speech are very coarse as compared to those used in music. For example, the final pitch rise that signals a question is typically larger than 7 semitones in both French and

English (e.g. Fitzsimons, Sheahan & Staunton, 2001), while most music across cultures are constructed with pitch variations in the order of 1 to 2 semi-tones (Vos and Troost, 1989). Thus, a temporal pitch deficit may exclusively compromise music perception and spare speech processing due to the fact that pitch changes used in music are more fine-grained and amusics cannot discriminate these small pitch changes, whereas they can discriminate the much larger pitch changes used in speech.

Summary and conclusion

The present work constitutes the first fMRI investigation of the neural correlates of pitch and time discrimination in congenital amusia. Contrary to expectation, amusics exhibited a similar pattern of BOLD activation as controls in the processing of changing pitch information. These results converge with other findings suggesting that the most salient pitch-based neural anomaly in the amusic brain lies outside the auditory cortex. In contrast, amusics did not show the same left-hemisphere auditory asymmetry as controls in the processing of temporally changing pitch information. We reasoned that these imaging data reflected that amusics may have problems to capture pitch changes when they are presented rapidly. Results from a subsequent behavioral experiment confirmed this hypothesis. We interpret these results as amusics having a more complex deficit than initially thought, involving pitch distance, pitch direction, and temporal resolution. Thus, we have found a brain and corresponding behavioral correlate of a deficit in the processing of temporally changing pitch information in amusics. We suggest that such a deficit may in part account for the musical problems seen in congenital amusia. It remains for future studies to further investigate the nature of this temporal pitch deficit.

References

Ashburner, J. and Friston, K. J., 2000. Voxel-based morphometry--the methods. Neuroimage. 11, 805-821.

Ayotte, J., Peretz, I. and Hyde, K., 2002. Congenital amusia: a group study of adults afflicted with a music-specific disorder. Brain. 125, 238-251.

Bella, S. D. and Peretz, I., 2003. Congenital amusia interferes with the ability to synchronize with music. Ann N Y Acad Sci. 999, 166-169.

Belin, P., Zatorre, R. J., Hoge, R., Evans, A. C. and Pike, B., 1999. Event-related fMRI of the auditory cortex. Neuroimage. 10, 417-429.

Belin, P., Zilbovicius, M., Crozier, S., Thivard, L., Fontaine, A., Masure, M. C. and Samson, Y., 1998. Lateralization of speech and auditory temporal processing. J Cogn Neurosci. 10, 536-540.

Boddaert, N., Chabane, N., Gervais, H., Good, C. D., Bourgeois, M., Plumet, M. H., Barthelemy, C., Mouren, M. C., Artiges, E., Samson, Y., Brunelle, F., Frackowiak, R. S. and Zilbovicius, M., 2004. Superior temporal sulcus anatomical abnormalities in childhood autism: a voxel-based morphometry MRI study. Neuroimage. 23, 364-369.

Boemio, A., Fromm, S., Braun, A. and Poeppel, D., 2005. Hierarchical and asymmetric temporal sensitivity in human auditory cortices. Nat Neurosci. 8, 389-395.

Boltz, M. G., 1998. Tempo discrimination of musical patterns: effects due to pitch and rhythmic structure. Percept Psychophys. 60, 1357-1373.

Brechmann, A. and Scheich, H., 2005. Hemispheric shifts of sound representation in auditory cortex with conceptual listening. Cereb Cortex. 15, 578-587.

Brust, J. C., 1980. Music and language: musical alexia and agraphia. Brain. 103, 367-392.

Cabeza, R., Anderson, N. D., Locantore, J. K. and McIntosh, A. R., 2002. Aging gracefully: compensatory brain activity in high-performing older adults. Neuroimage. 17, 1394-1402.

Collins, D. L., Neelin, P., Peters, T. M. and Evans, A. C., 1994. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. J Comput Assist Tomogr. 18, 192-205.

Di Pietro, M., Laganaro, M., Leemann, B. and Schnider, A., 2004. Receptive amusia: temporal auditory processing deficit in a professional musician following a left temporo-parietal lesion. Neuropsychologia. 42, 868-877.

Dowling, W., and Harwood, D. 1986. Music cognition. New York: Academic Press.

Ehrle, N., Samson, S. and Baulac, M., 2001. Processing of rapid auditory information in epileptic patients with left temporal lobe damage. Neuropsychologia. 39, 525-531.

Fitzsimons, M., Sheahan, N. and Staunton, H., 2001. Gender and the integration of acoustic dimensions of prosody: implications for clinical studies. Brain Lang. 78, 94-108.

Formisano, E., Kim, D. S., Di Salle, F., van de Moortele, P. F., Ugurbil, K. and Goebel, R., 2003. Mirror-symmetric tonotopic maps in human primary auditory cortex. Neuron. 40, 859-869.

Foxton, J. M., Dean, J. L., Gee, R., Peretz, I. and Griffiths, T. D., 2004. Characterization of deficits in pitch perception underlying 'tone deafness'. Brain. 127, 801-810.

Fraisse, P. 1974. Psychologie du rythme, Presses Universitaires de France.

Geschwind, N. 1984. The brain of a learning-disabled individual. Ann. Dyslexia. 34, 319–327.

Gougoux, F., Lepore, F., Lassonde, M., Voss, P., Zatorre, R. J. and Belin, P., 2004. Neuropsychology: pitch discrimination in the early blind. Nature. 430, 309.

Grady, C. L., Bernstein, L. J., Beig, S. and Siegenthaler, A. L., 2002. The effects of encoding task on age-related differences in the functional neuroanatomy of face memory. Psychol Aging. 17, 7-23.

Grady, C. L., McIntosh, A. R., Rajah, M. N., Beig, S. and Craik, F. I., 1999. The effects of age on the neural correlates of episodic encoding. Cereb Cortex. 9, 805-814.

Grant-Allen. 1878. Note-deafness. Mind 10, 157-167

Griffiths, T. D., Johnsrude, I., Dean, J. L. and Green, G. G., 1999. A common neural substrate for the analysis of pitch and duration pattern in segmented sound? Neuroreport. 10, 3825-3830.

Halpern, A. R. and Zatorre, R. J., 1999. When that tune runs through your head: a PET investigation of auditory imagery for familiar melodies. Cereb Cortex. 9, 697-704.

Hartmann, W.M., Rakerd, B., and Packard, T.N. 1985. On measuring the frequency-difference limen for short tones Perception & psychophysics 38, 199-207.

Henke, W.L. 1976. An interactive dialogue language for time signal processing. Cambridge (MA): MIT Research Laboratory of Electronics.

Hyde, K.L., Zatorre, R.J., and Peretz, I. 2003. Evidence for the specific role of the right auditory cortex in fine pitch resolution. Presented at the 9th International Conference on Functional Mapping of the Human Brain, June 19-22, New York. Neuroimage, Vol. 19(2).

Hyde, K. L. and Peretz, I., 2004. Brains that are out of tune but in time. Psychol Sci. 15, 356-360.

Hyde, K.L., & Peretz, I. 2005. Congenital amusia: Impaired musical pitch but intact musical time. In: Syka, J. and Merzenich, M. (Ed.) Plasticity and signal representation in the auditory system. (pp. 291-296). New York, NY, US: Springer Publishing Co. x, 416 pp.

Hyde, K.L., Zatorre, R.J., Griffiths, T.D., Lerch, J.P. & Peretz, I. (2005). The Brain Morphometry of Congenital Amusic Individuals. Presented at the 11th International Conference on Functional Mapping of the Human Brain, June 12-16, Toronto. Neuroimage.

Johnsrude, I. S., Penhune, V. B. and Zatorre, R. J., 2000. Functional specificity in the right human auditory cortex for perceiving pitch direction.

Brain. 123 (Pt 1), 155-163.

Kalmus, H. and Fry, D. B., 1980. On tune deafness (dysmelodia): frequency, development, genetics and musical background. Ann Hum Genet. 43, 369-382.

Koelsch, S., Gunter, T. C., v Cramon, D. Y., Zysset, S., Lohmann, G. and Friederici, A. D., 2002. Bach speaks: a cortical "language-network" serves the processing of music. Neuroimage. 17, 956-966.

Langers, D. R., Backes, W. H. and van Dijk, P., 2003. Spectrotemporal features of the auditory cortex: the activation in response to dynamic ripples. Neuroimage. 20, 265-275.

Liegeois-Chauvel, C., de Graaf, J. B., Laguitton, V. and Chauvel, P., 1999. Specialization of left auditory cortex for speech perception in man depends on temporal coding. Cereb Cortex. 9, 484-496.

Liegeois-Chauvel, C., Giraud, K., Badier, J. M., Marquis, P. and Chauvel, P., 2001. Intracerebral evoked potentials in pitch perception reveal a functional asymmetry of the human auditory cortex. Ann N Y Acad Sci. 930, 117-132.

Mavlov, L., 1980. Amusia due to rhythm agnosia in a musician with left hemisphere damage: a non-auditory supramodal defect. Cortex. 16, 331-338.

Milner BA (1962) Laterality effects in audition. In: Interhemispheric relations and cerebral dominance (Mountcastle V, ed.), pp177–195. Baltimore, MD: Johns Hopkins University Press.

Moelants, Dirk (2002d). Preferred tempo reconsidered. In C. Stevens, D. Burnham, G. McPherson, E. Schubert, J. Renwick (Eds.) Proceedings of the 7th International Conference on Music Perception and Cognition, Sydney, 2002 (pp. 580-583). Adelaide: Causal Productions.

Moelants, Dirk (2003a). Dance music, movement and tempo preferences. In R. Kopiez, A.C. Lehmann, I. Wolther and C. Wolf (Eds.) Proceedings of the 5th triennial ESCOM Conference (pp. 649-652), Hanover: University of Music and Drama.

Murayama, J., Kashiwagi, T., Kashiwagi, A. and Mimura, M., 2004.

Impaired pitch production and preserved rhythm production in a right brain-damaged patient with amusia. Brain Cogn. 56, 36-42.

Naatanen, R. and Picton, T., 1987. The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. Psychophysiology. 24, 375-425.

Nielson, K. A., Langenecker, S. A. and Garavan, H., 2002. Differences in the functional neuroanatomy of inhibitory control across the adult life span. Psychol Aging. 17, 56-71.

Patterson, R. D., Uppenkamp, S., Johnsrude, I. S. and Griffiths, T. D., 2002. The processing of temporal pitch and melody information in auditory cortex. Neuron. 36, 767-776.

Penhune, V. B., Zatorre, R. J., MacDonald, J. D. and Evans, A. C., 1996. Interhemispheric anatomical differences in human primary auditory cortex: probabilistic mapping and volume measurement from magnetic resonance scans. Cereb Cortex. 6, 661-672.

Peretz, I., 1990. Processing of local and global musical information by unilateral brain-damaged patients. Brain. 113 (Pt 4), 1185-1205.

Peretz, I., 2001. Brain specialization for music. New evidence from congenital amusia. Ann N Y Acad Sci. 930, 153-165.

Peretz, I., Ayotte, J., Zatorre, R. J., Mehler, J., Ahad, P., Penhune, V. B. and Jutras, B., 2002. Congenital amusia: a disorder of fine-grained pitch discrimination. Neuron. 33, 185-191.

Peretz, I., Champod, A. S. and Hyde, K., 2003. Varieties of musical disorders. The Montreal Battery of Evaluation of Amusia. Ann N Y Acad Sci. 999, 58-75.

Peretz, I. and Hyde, K. L., 2003. What is specific to music processing? Insights from congenital amusia. Trends Cogn Sci. 7, 362-367.

Peretz, I. and Kolinsky, R., 1993. Boundaries of separability between melody and rhythm in music discrimination: a neuropsychological perspective. Q J Exp Psychol A. 46, 301-325.

Peretz, I., Brattico, E. and Tervaniemi, M., 2005. Abnormal electrical brain responses to pitch in congenital amusia. Ann Neurol. 58, 478-482.

Perry, D. W., Zatorre, R. J., Petrides, M., Alivisatos, B., Meyer, E. and Evans, A. C., 1999. Localization of cerebral activity during simple singing. Neuroreport. 10, 3979-3984.

Phillips, D. P. and Farmer, M. E., 1990. Acquired word deafness, and the temporal grain of sound representation in the primary auditory cortex. Behav Brain Res. 40, 85-94.

Piccirilli, M., Sciarma, T. and Luzzi, S., 2000. Modularity of music: evidence from a case of pure amusia. J Neurol Neurosurg Psychiatry. 69, 541-545.

Poeppel, D. 2003. The analysis of speech in different temporal integration windows: cerebral lateralization as 'asymmetric sampling in time'. Speech Communication 41, 245-255.

Robin, D.A., Tranel, D., Damasio, H. 1990. Auditory perception of temporal and spectral events in patients with focal left and right cerebral lesions. Brain Lang 39, 539–555.

Schönwiesner, M., Rubsamen, R. and von Cramon, D. Y., 2005. Hemispheric asymmetry for spectral and temporal processing in the human antero-lateral auditory belt cortex. Eur J Neurosci. 22, 1521-1528.

Schuppert, M., Munte, T. F., Wieringa, B. M. and Altenmuller, E., 2000. Receptive amusia: evidence for cross-hemispheric neural networks underlying music processing strategies. Brain. 123 Pt 3, 546-559.

Tallal, P., Miller, S. and Fitch, R. H., 1993. Neurobiological basis of speech: a case for the preeminence of temporal processing. Ann N Y Acad Sci. 682, 27-47.

Talavage, T. M., Sereno, M. I., Melcher, J. R., Ledden, P. J., Rosen, B. R. and Dale, A. M., 2004. Tonotopic organization in human auditory cortex revealed by progressions of frequency sensitivity. J Neurophysiol. 91, 1282-1296.

Tervaniemi, M., Medvedev, S. V., Alho, K., Pakhomov, S. V., Roudas, M. S., Van Zuijen, T. L. and Naatanen, R., 2000. Lateralized automatic auditory processing of phonetic versus musical information: a PET study. Hum Brain Mapp. 10, 74-79.

Tillmann, B., Janata, P. and Bharucha, J. J., 2003. Activation of the inferior frontal cortex in musical priming. Brain Res Cogn Brain Res. 16, 145-161.

Trainor, L. J. and Trehub, S. E., 1994. Key membership and implied harmony in Western tonal music: developmental perspectives. Percept Psychophys. 56, 125-132.

Warren, J. D. and Griffiths, T. D., 2003. Distinct mechanisms for processing spatial sequences and pitch sequences in the human auditory brain. J Neurosci. 23, 5799-5804.

Warren, R. M., Gardner, D. A., Brubaker, B. S. and Bashford, J. A., 1991. Melodic and nonmelodic sequences of tones: Effects of duration on perception. Music Perception. 8, 277-289.

Warrier, C. M. and Zatorre, R. J., 2004. Right temporal cortex is critical for utilization of melodic contextual cues in a pitch constancy task. Brain. 127, 1616-1625.

Watkins, K. E., Vargha-Khadem, F., Ashburner, J., Passingham, R. E., Connelly, A., Friston, K. J., Frackowiak, R. S., Mishkin, M. and Gadian, D. G., 2002. MRI analysis of an inherited speech and language disorder: structural brain abnormalities. Brain. 125, 465-478.

Westbury, C. F., Zatorre, R. J. and Evans, A. C., 1999. Quantifying variability in the planum temporale: a probability map. Cereb Cortex. 9, 392-405.

Worsley, K. J., Liao, C. H., Aston, J., Petre, V., Duncan, G. H., Morales, F. and Evans, A. C., 2002. A general statistical analysis for fMRI data. Neuroimage. 15, 1-15.

Yamasaki, T., Goto, Y., Taniwaki, T., Kinukawa, N., Kira, J. and Tobimatsu, S., 2005. Left hemisphere specialization for rapid temporal

processing: a study with auditory 40 Hz steady-state responses. Clin Neurophysiol. 116, 393-400.

Vinckenbosch, E., Robichon, F. and Eliez, S., 2005. Gray matter alteration in dyslexia: converging evidence from volumetric and voxel-by-voxel MRI analyses. Neuropsychologia. 43, 324-331.

Vos, P.G., and Troost, J.M. 1989. Ascending and descending melodic intervals: Statistical findings and their perceptual relevance. Music Perception, 6, 383-396.

Zatorre, R. J., 1988. Pitch perception of complex tones and human temporal-lobe function. J Acoust Soc Am. 84, 566-572.

Zatorre, R. J. and Belin, P., 2001. Spectral and temporal processing in human auditory cortex. Cereb Cortex. 11, 946-953.

Zatorre, R. J., Belin, P. and Penhune, V. B., 2002. Structure and function of auditory cortex: music and speech. Trends Cogn Sci. 6, 37-46.

Zatorre, R. J., Evans, A. C. and Meyer, E., 1994. Neural mechanisms underlying melodic perception and memory for pitch. J Neurosci. 14, 1908-1919.

Table 1:

Characteristics	Amusics (n=9)	Controls (n=9)	t-test
Age in years	56.7 (7.0)	53.1 (5.9)	n.s.
Gender	7F, 2M	5F, 4M	
Education in years	16.0 (1.3)	16.0 (2.0)	n.s.
Musical battery (MBEA)	64.2 (5.9)	88.4 (6.6)	$P < 0.001$
Pitch discrimination*	77.3 (8.4)	99.5 (0.4)	$P < 0.001$
Time discrimination*	71.7 (2.5)	74.8 (1.6)	n.s.

Characteristics of participants, percentage global score (averaged over six tests) on Montreal Battery of Evaluation of Amusia (MBEA), percentage of correct responses on pitch and time discrimination tasks (averaged over 360 trials), and significance levels on corresponding *t* tests. Standard deviations are in parentheses. *Scores are averaged over n=7 amusic subjects and n=6 controls.

Table 2:

Contrast	Controls (n=9) Region of peak	BA	x	y	z	t	Amusics (n=9) Region of peak	BA	x	y	z	t
All conditions - baseline of silence												
	R HG	41	44	-30	16	5.5	R HG	41	40	-30	12	8.3
	R anterior STG	42	60	-8	2	4.7						
	R anterior STG	42	66	-8	2	4.7						
	R PT	42	64	-26	12	4.3	R PT	42	66	-28	14	6.6
	L anterior STG	42	-70	-6	4	3.7	L PT	42	-64	-16	2	5.1
							L PT	42	-50	-14	4	5.9
	L HG	41	-36	-30	16	3.7	L HG	41	-38	-32	14	8.4
All pitch-variation conditions - fixed pitch												
	L PT	42	-64	-26	8	3.8	L PT	42	-54	-24	8	4.0
	R PT	42	62	-18	0	3.6	R anterior STG	42	58	-8	6	4.5
	L PT	42	-50	-24	6	3.5	L PT	42	-50	-28	10	4.0
							L PT	42	-56	-12	4	3.7
	L anterior STG	42	-58	0	-2	3.5	L anterior STG	42	-56	-6	4	3.9
							L anterior STG	42	-56	-6	14	3.8
							R HG	41	44	-30	10	3.6
Pitch covariation												
	R PT	42	56	-12	4	3.5	R PT	42	60	-18	8	8.2
	L PT	42	-56	-26	10	3.4	L PT	42	-54	-14	6	5.7
							L HG	41	-44	-30	8	6.7
Fastest temporal rate - fixed pitch												
	L HG	41	-48	-22	6	5.1	L HG	41	-44	-32	6	3.8
	R PT	42	56	-18	6	3.3	R HG	41	48	-28	8	5.5
Fastest - slowest temporal rate												
	L HG	41	-44	-20	4	4.1	L HG	41	-44	-28	12	3.1
	R HG	41	40	-26	14	3.2	R HG	41	48	-24	8	4.1
							R PT	42	66	-12	2	5.1
							L PT	42	-56	-16	0	3.3
Time covariation												
	L HG	41	-44	-22	6	5.3	L HG	41	-44	-28	10	6.9
	L HG	41	-48	-18	8	5.3						
	L posterior STS	21/22	-40	-32	18	4.3	L PT	42	-56	-16	0	5.7
	R anterior STG	42	42	-8	4	4.1	R PT	42	60	-14	0	5.6
	R HG	41	42	-26	14	4.0	R HG	41	50	-22	6	6.0

FMRI results for within-group analyses for amusics and controls. For each peak, the brain region and the corresponding Brodmann area (BA) are given. The stereotaxic coordinates of the peak activations are given according to Talairach/MNI space, as well as the *t*-value. For the subtractions, a positive *t*-value reflects an increased BOLD response, and for the covariations, it reflects a positive linear trend of the BOLD signal as a function of either increasing pitch distance or temporal rate. Results are significant at $P < 0.05$ (corrected) at $t > 5.0$ for a whole-brain volume, and $t > 3.5$ for the ROI volume. L, left; R, right; HG, Heschl's Gyrus; PT, Planum Temporale; STG, superior temporal gyrus; STS, superior temporal sulcus.

Figure legends:

Figure 1: Schematic of a pitch pattern used in the fMRI study.

Figure 2: Schematic of the fMRI scanning paradigm showing the three conditions, pitch, temporal rate, and baseline of silence (in no particular order) (adapted from Belin et al, 1999).

Figure 3: fMRI results for the pitch conditions, within-group analyses, for controls and amusics. In A), are the results for the pitch variation - fixed pitch contrast, and the pitch covariation superimposed on the average anatomical MRI of the corresponding group. Images are shown as horizontal sections and yellow arrows point to the left and right PT in each brain image. In the contrast image, these right and left peaks reflect areas of increased BOLD activation, and in the covariation image, these peaks reflect areas with a positive linear trend of the BOLD signal with increasing pitch distance. These peaks were significant at $P < 0.05$ (corrected) at the *ROI threshold (see Table 2 for corresponding *t*-statistics and stereotaxic coordinates). In B), are the significant positive correlations of BOLD signal change as a function of increasing pitch distance at the left and right PT peaks and corresponding Pearson *r* values. In C) are the average slopes of the BOLD signal at the left and right PT peaks.

Figure 4: fMRI results for the time conditions, within-group analyses, for controls and amusics. In A), are the results for fastest - slowest temporal rate contrast, and time covariation superimposed on the average anatomical MRI of the corresponding group. Images are shown as horizontal sections and yellow arrows point to the left and right HG in each brain image. In the contrast image, these right and left peaks reflect areas of increased BOLD activation, and in the covariation image, these peaks reflect areas with a positive linear trend of the BOLD signal with faster temporal rates. These

peaks were significant at $P < 0.05$ (corrected) at the *ROI threshold and the **whole-brain threshold (see Table 2 for corresponding *t*-statistics and stereotaxic coordinates). In B), are the positive correlations of BOLD signal change as a function of increasing temporal rate at the left and right HG peaks and corresponding Pearson *r* values. In C) are the average slopes of the BOLD signal at the left and right HG peaks.

Figure 5: fMRI results for the time conditions, between-group analyses considering amusics – controls. In A), are the results for the contrasts of fastest temporal rate – fixed pitch, the fastest – slowest temporal rate contrasts, and time covariation, superimposed on the average anatomical MRI of all subjects. Images are shown as horizontal sections and the yellow arrow in all images points to the left HG peak. In the contrast images, at this left HG peak, controls had stronger BOLD activation relative to amusics [$*P < 0.05$ (corrected) at ROI threshold]. In the covariation image, at this left HG peak, controls had a stronger linear trend of the BOLD signal over all temporal rates relative to amusics. In B) are the average slopes of the BOLD signal for controls versus amusics at the left and right HG peaks.

Figure 6: Behavioral results for pitch-tempo *direction* (A) and *discrimination* (B) conditions for controls and amusics. Percentage correct for each pitch level (P) in cents, at each temporal rate (T) in ms (from slowest T of 367 ms to fastest T of 22 ms). Error bars correspond to standard error.

Figure 1:

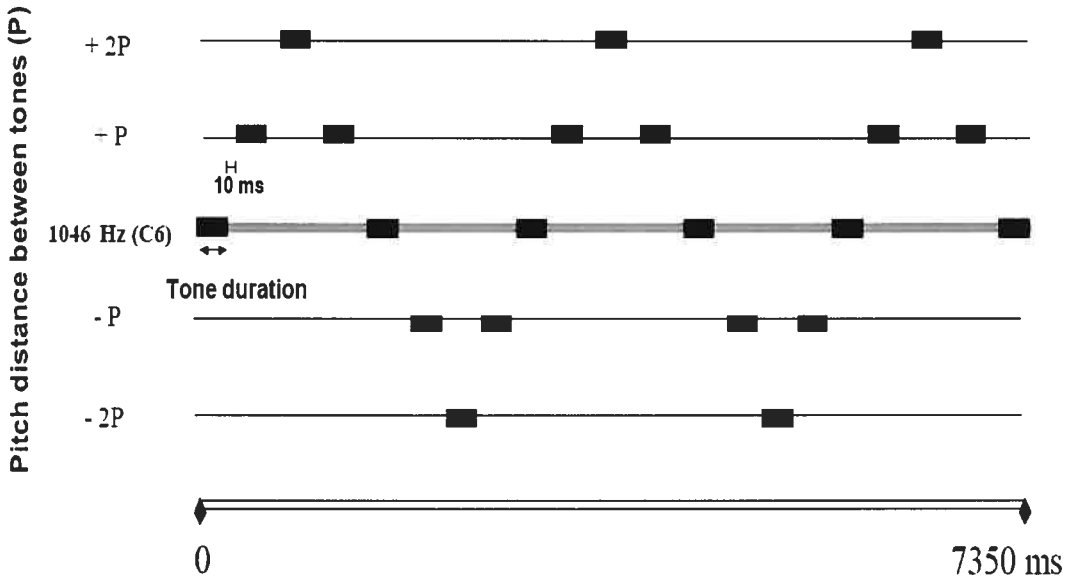

Pitch distance between tones (P)
+ 2P
+ P
10 ms
1046 Hz (C6)
Tone duration
- P
- 2P
0
7350 ms

Figure 2:

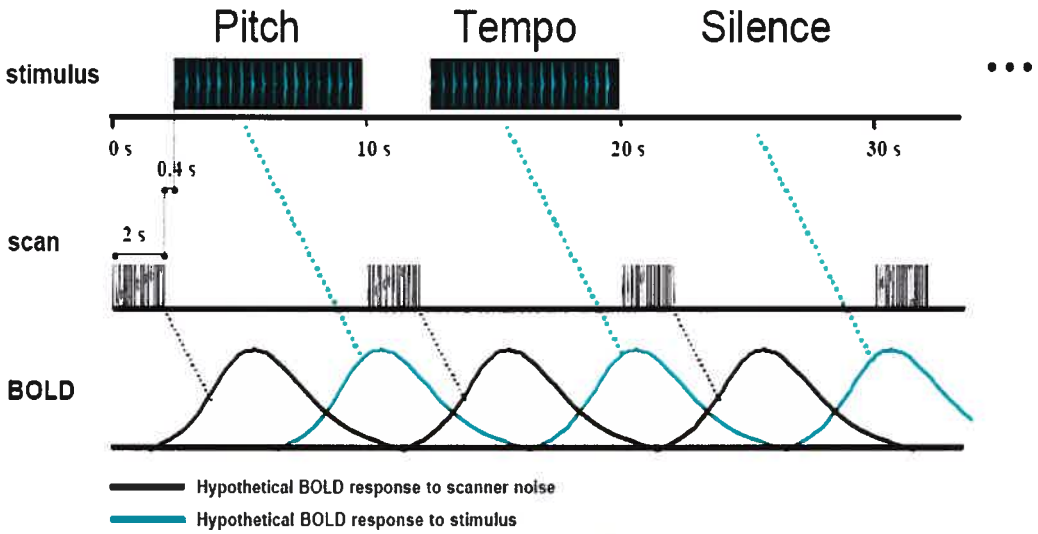

Pitch
Tempo
Silence
stimulus
0 s
10 s
20 s
30 s
0.4 s
2 s
scan
BOLD
Hypothetical BOLD response to scanner noise
Hypothetical BOLD response to stimulus

Figure 3:

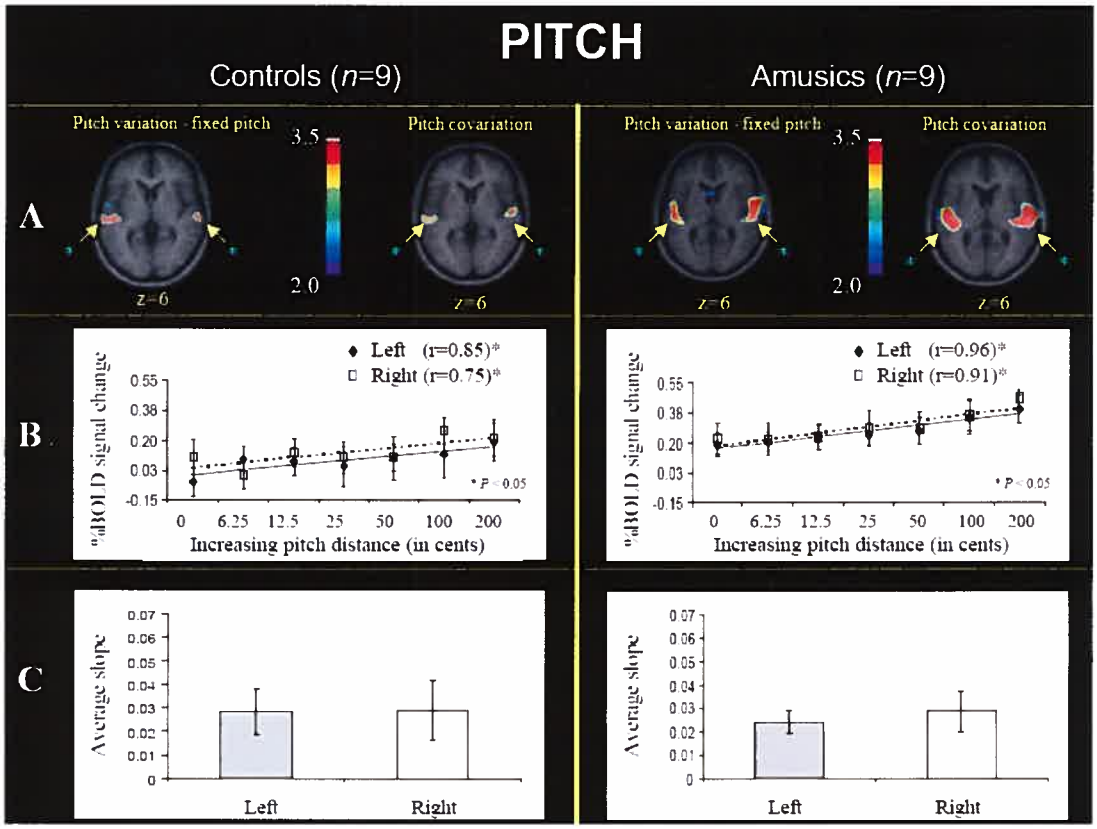

PITCH
Controls (n=9)
Amusics (n=9)
A
Pitch variation - fixed pitch
Pitch covariation
3.5
2.0
z=6
B
Left (r=0.85)*
Right (r=0.75)*
Left (r=0.96)*
Right (r=0.91)*
%dBOLD signal change
0.55
0.38
0.20
0.03
-0.15
0
6.25
12.5
25
50
100
200
Increasing pitch distance (in cents)
* P < 0.05
C
Average slope
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
Left
Right

Figure 4:

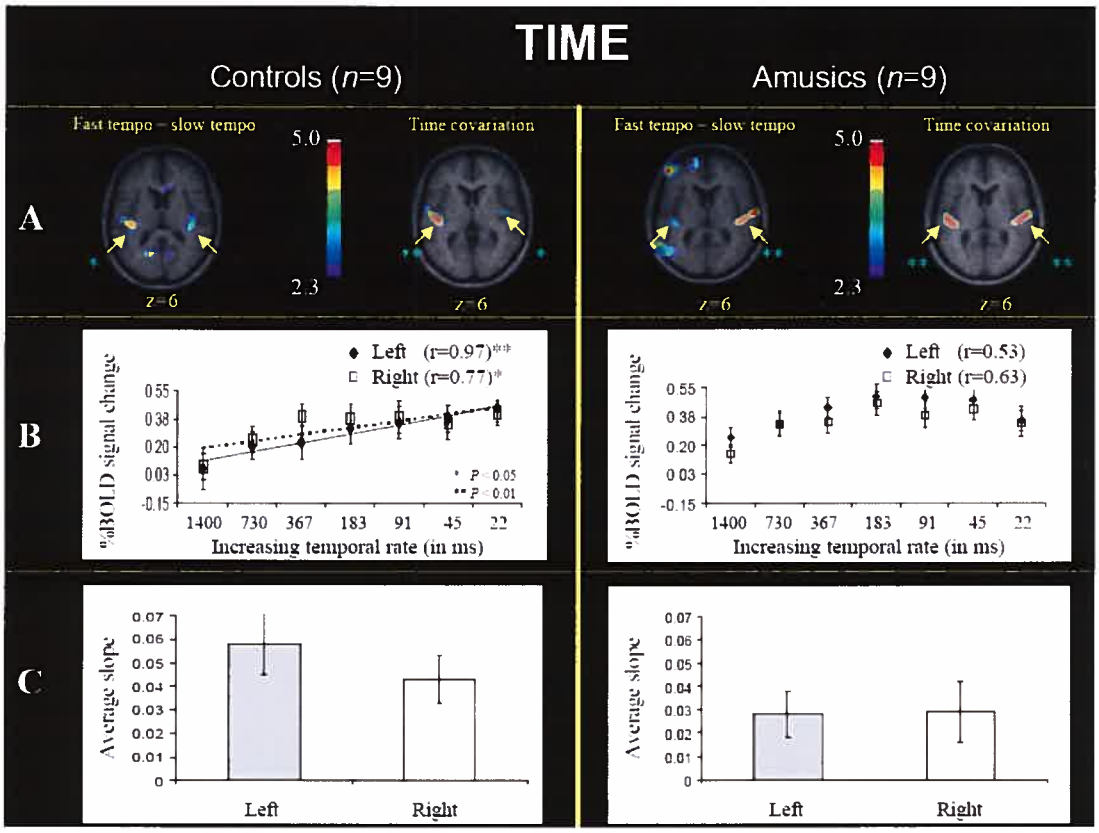

TIME
Controls (n=9)
Amusics (n=9)
A
Fast tempo – slow tempo
Time covariation
5.0
2.3
z=6
B
%BOLD signal change
Left (r=0.97)**
Right (r=0.77)*
* P < 0.05
** P < 0.01
1400 730 367 183 91 45 22
Increasing temporal rate (in ms)
Left (r=0.53)
Right (r=0.63)
C
Average slope
Left
Right

Figure 5:

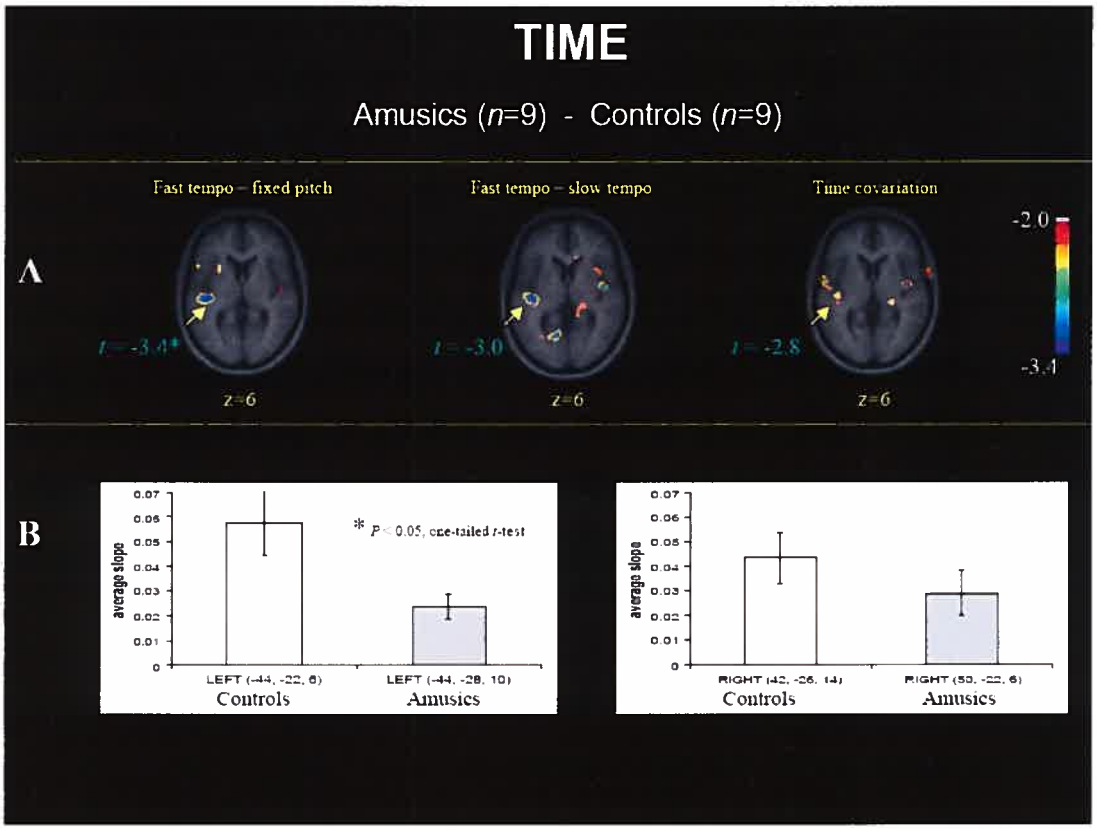
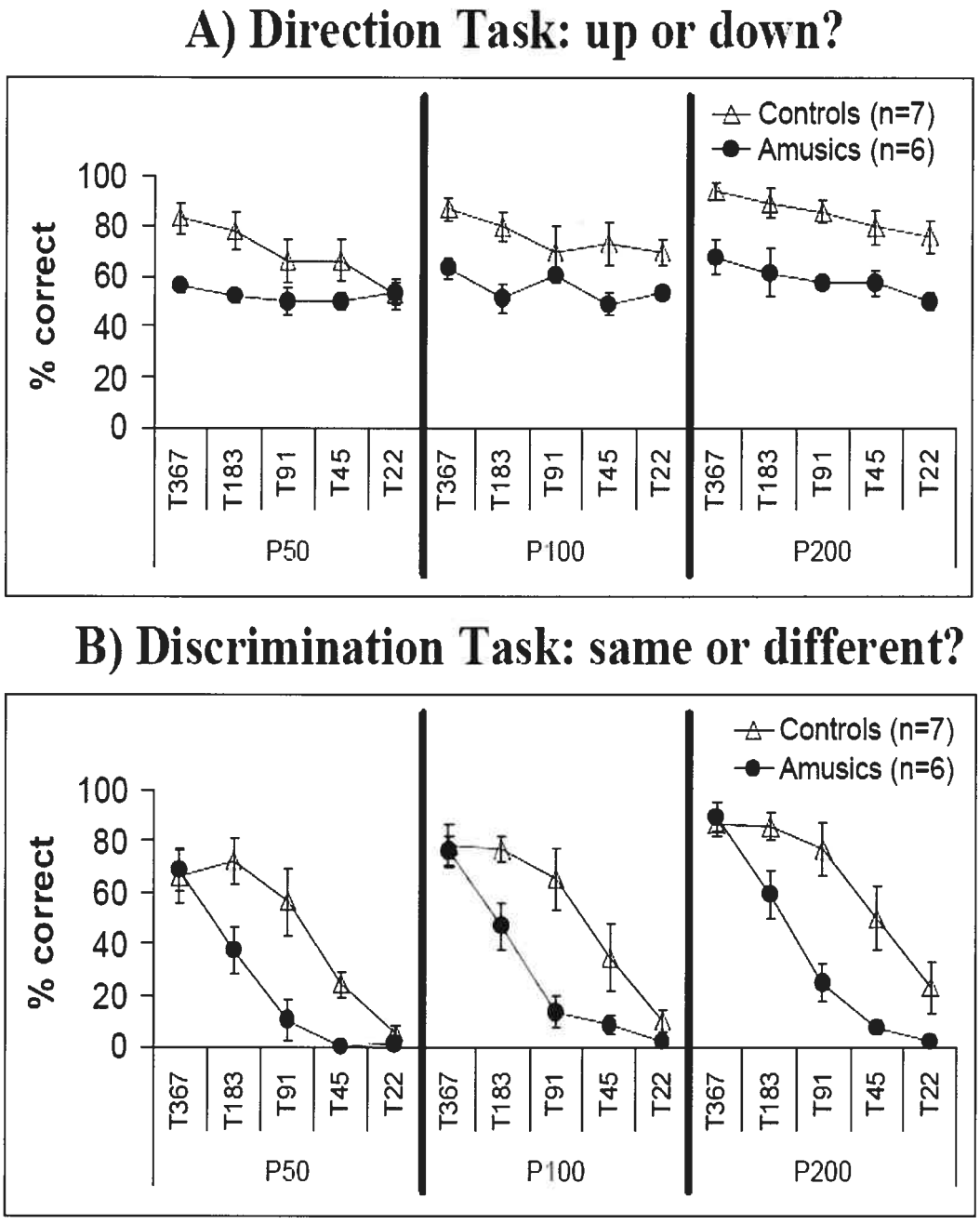

TIME
Amusics (n=9) - Controls (n=9)
A
Fast tempo – fixed pitch
Fast tempo – slow tempo
Time covariation
t = -3.4*
t = -3.0
t = -2.8
z=6
z=6
z=6
-2.0
-3.4
B
average slope
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
* P < 0.05, one-tailed t-test
LEFT (-44, -22, 6)
LEFT (-44, -28, 10)
Controls
Amusics
RIGHT (42, -26, 14)
RIGHT (50, -22, 6)
Controls
Amusics

Figure 6:


A) Direction Task: up or down?
Controls (n=7)
Amusics (n=6)
% correct
100
80
60
40
20
0
T367
T183
T91
T45
T22
P50
P100
P200
B) Discrimination Task: same or different?
Controls (n=7)
Amusics (n=6)
% correct
100
80
60
40
20
0
T367
T183
T91
T45
T22
P50
P100
P200

FOURTH ARTICLE:
MORPHOMETRY OF THE AMUSIC BRAIN: A TWO-SITE STUDY

Morphometry of the Amusic Brain: a Two-Site Study

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Summary

Congenital amusia (or tone-deafness) is a lifelong disability that prevents otherwise normal functioning individuals from developing basic musical skills. Behavioral evidence indicates that congenital amusia is due to a severe deficit in pitch processing. The neural correlates of this condition are presently unknown. Here, voxel-based morphometry (VBM) was used to detect brain anatomical differences in amusic individuals relative to musically-intact controls, in two independent samples of subjects. The results were consistent across samples in highlighting a reduction in white matter concentration in the right inferior frontal gyrus of amusic individuals. This anatomical anomaly was related to pitch-based musical tasks. Thus, the data point to the integrity of white-matter tracts in right frontal brain areas as being key in acquiring normal musical competence.

Introduction

Human societies have always produced and enjoyed music, but about four percent of the general population is not able to do so (Kalmus and Fry, 1980). These individuals are likely afflicted with congenital amusia (Peretz & Hyde, 2003). This condition is characterized by impairments that are specific to the perception and production of music. Amusic persons are unable to recognize familiar tunes, and are unaware when they sing 'out-of-tune', but have normal neurological history, audition, education, intelligence and memory (Ayotte et al, 2002). Collective behavioral evidence indicates that a severe and specific deficit in the sequential processing of pitch information is at the root of congenital amusia (Ayotte et al, 2002; Hyde and Peretz, 2004; Foxton et al, 2004). The neural correlates of this condition are presently unknown.

In order to uncover structural brain differences in amusics relative to musically-intact controls, we used voxel-based morphometry (VBM). VBM is a computerized, automated procedure that allows one to search throughout the whole brain on a voxel-wise basis for differences in local concentration of brain tissue between groups (Ashburner and Friston, 2000). This technique has been effective in revealing brain abnormalities in a number of developmental disorders, including speech disorders (Watkins et al, 2002), dyslexia (Vinckenbosch et al, 2005), and autism (Boddaert et al, 2004).

Here, we applied VBM in two independent samples, with T1-weighted magnetic resonance images (MRI) obtained in Montreal (Canada) and in Newcastle (UK). We used a hypothesis-generating / testing approach across the Montreal and Newcastle samples since we could not merge the data due to inherent cross-scanner incompatibilities (Ashburner and Friston, 2000). The Montreal sample, comprised of 13 amusic adults (mean age 56, SD 11 years) and 22 controls (mean age 55, SD 6 years), was the primary sample from which we generated hypotheses since it was the first sample to be

analyzed. These hypotheses were then tested in the Newcastle sample, comprised of 8 amusics (mean age 54, SD 12 years) and 7 controls (mean age 54, SD 5 years). All amusic subjects had been thoroughly evaluated on previous testing sessions (Ayotte et al, 2002; Foxton et al, 2004), and identical criteria were used for subject selection in both samples.

All amusics had normal intellectual, memory and language skills, but were impaired relative to normal controls on the Montreal Battery of Evaluation of Amusia (MBEA; Peretz et al, 2003). Subjects were considered amusic if their global score on the MBEA was below the cut-off score determined in a previous validation study (Peretz et al, 2003). Here, the MBEA also served to relate brain anatomy to performance. The battery involves six tests. One test evaluates the sense of meter, and the final test is one of recognition memory. The other four tests assess discrimination. Three of these assess the ability to discriminate melodic changes (that violate key, pitch direction or pitch distance) and one tests rhythmic discrimination (by changing temporal grouping). Both the melodic and rhythmic tests use a "same-different" discrimination task, with the same set of novel but conventional sounding music. As can be seen in Figure 1, all amusic participants were severely impaired relative to controls on the melodic tests while about half of them showed normal performance on the rhythmic test. This is consistent with findings showing that congenital amusia is largely a pitch-based condition (Hyde and Peretz, 2004; Foxton et al, 2004).

All the amusic and matched control individuals were scanned in a 1.5 Tesla MR scanner at their respective site, but with the same acquisition parameters. We carried out three different types of analyses on both the Montreal and Newcastle MRI data. First, we performed a group comparison to identify brain regions that differed in terms of white matter (WM) or grey matter (GM) concentration between amusics and controls. We next performed correlational analyses to detect brain regions where WM concentration

correlates with performance on the musical tests of the MBEA. Given that each test of the musical battery assesses a different aspect of music processing, and that there exists some variability in performance, we considered each test separately. Lastly, in order to specify the common areas of WM differences across the samples and analyses, we performed conjunction analyses by spatially overlapping the thresholded results from the two samples for the group and correlational analyses. This analysis is independent of the order in which the samples are considered since it is a logical "AND" operation.

Results and Discussion

The results from the group comparison in the Montreal sample yielded four candidate brain regions where amusics showed less WM than controls. Three of these regions were found in the right inferior frontal gyrus (IFG), and one in the left IFG. However, only one of these regions, corresponding to the pars orbitalis of the right IFG in the vicinity of Brodmann areas (BA) 47 and 11 ($t = -2.7$, $P < 0.05$, uncorrected), was significant in the Newcastle sample [$t = -5.7$, $P < 0.05$, corrected at VOI 20,261 mm^3)] (Figure 2a, left and middle panels). There were no other significant peaks in the Newcastle sample. There were also candidate peaks of increased concentration of WM in the Montreal sample. However, none of these were confirmed in the Newcastle sample. Thus, these peaks most likely correspond to false positives and are not reported here. There were no significant peaks of increased WM in the Newcastle sample alone.

As in the group comparison, the voxel-based correlations with WM concentration and performance on two musical tests in the Montreal sample, revealed the same rIFG region. WM concentration in this region was positively correlated with both the melodic key-violation test ($t = 2.4$, $P < 0.05$, uncorrected; Figure 2b, left panel), and with the memory test ($t = 2.8$, $P <$

0.05, uncorrected; Supplementary Figure 1b, left panel), but not with the other four musical tests. The same analyses in the Newcastle sample confirmed the positive correlation of WM concentration in the rIFG with both the key-violation test ($t = 6.6$, $P < 0.01$, corrected at VOI 8,807 mm^3; Figure 2b, middle panel), and the memory test ($t = 4.1$, $P < 0.05$, corrected at VOI 1215 mm^3; Supplementary Figure 1b, middle panel). There were no other significant peaks in the Newcastle sample in any of the musical test correlations. To illustrate this relationship between brain morphometry and behavior, we plotted the WM concentration obtained at the rIFG peak for each subject as a function of their behavioral scores on the key-violation and memory tests. As shown in Figure 2c, WM concentration increased with increasing performance score on the key-violation test, in both the Montreal ($r = 0.4$, $P < 0.05$) and Newcastle samples ($r = 0.74$, $P < 0.05$). This was also true in the memory test ($r = 0.4$ and 0.75, $P < 0.05$, for the Montreal and Newcastle samples, respectively; Supplementary Figure 1c).

The conjunction analyses revealed that the rIFG region was common to both samples within three millimetres along the x, y, and z planes, respectively. The striking convergence of this result across samples can be seen for both the group (Figure 2a and Supplementary Figure 1a, right panels) and correlational analyses (Figure 2b and Supplementary Figure 1b, right panels), as well as across these analyses (Figures 2d and Supplementary Figure 1d). In order to further specify where the conjunction occurs relative to the regions delineated in each sample, we quantified what proportion the conjunction represents relative to the total area in each sample. The conjunction represents 34% of the Montreal sample area, and 19% of the Newcastle area (Figure 3). Thus, the conjunction is not merely an edge artifact of the regions defined independently in each sample.

The VBM results for the WM differences were clearly consistent across samples in pointing to a significant decrease in WM in the rIFG of amusic

individuals. An analysis of GM revealed concentration differences in approximately the same brain regions as the WM differences, but in the opposite direction. Such an inverse relationship between WM and GM is typically found in brain regions in which WM and GM tissues are in close proximity, as in the cortex. This is primarily due to the partial-volume effect where a given voxel may contain both WM and GM (Ashburner and Friston, 2000). In the present study, we propose that the rIFG peak more likely corresponds to WM given its neuroanatomical location in terms of its depth (along the z-plane) (Duvernoy, 1991), and that deeper brain structures typically consist of WM.

Support for this interpretation comes from a functional perspective. Several prior studies conducted with musically normal subjects have identified right inferior frontal regions as central to the active retention of pitch in melodies (Zatorre et al, 1994) and to the interpretation of pitch in terms of musical keys (Koelsch et al, 2002; Tillmann et al, 2003). Thus, finding a decrease in WM tissue in the rIFG of amusic individuals that is related to performance in both musical key discrimination and memory, fits nicely with current knowledge of the brain organization for musical pitch processing. Indeed, encoding pitch in terms of musical keys is conceived as an essential component in music processing. It affords a hierarchical organization of pitch events and thereby facilitates music processing by creating expectancies and feelings of surprise or satisfaction. This ability to map pitches onto keys appears early in development (Trainor and Trehub, 1994), and is instrumental in music memory (e.g., Hébert & Peretz, 1997). Thus, a defect in musical pitch encoding may account for the highly selective nature of congenital amusia. Furthermore, it is consistent with the view that this music-specific condition may have a genetic component. Indeed, the melodic key-violation test that correlates so highly with WM concentration in the rIFG area, is similar to a task that has been shown to have a genetic element (Drayna et al, 2001). Thus, the present results fit with the idea that reduced connectivity with this

region may be related to a genetic component that would contribute to problems in the musical encoding of pitch.

The idea of a reduced connectivity to the rIFG region raises an interesting question as to whether the WM differences observed here are a consequence of anomalies in other parts of the auditory system. It is likely that other neural differences will be uncovered with further analyses, particularly in auditory cortical regions. Accordingly, we do not claim to have found a cause or the origin of congenital amusia. We rather conceive the decrease in WM found in the rIFG of amusic individuals as a consequence of an anomalous wiring of the connections to the auditory cortex (Hackett et al, 1999). Moreover, the data suggest that normal acquisition of basic musical abilities depend upon structural integrity of a right frontotemporal pathway.

In conclusion, one salient difference in the congenital amusic brain that is biologically sensible is the presence of an impoverished communication in a right-hemisphere based network involving the inferior frontal cortex and subserving the processing of pitch in musical contexts. This finding has implications for the understanding of normal acquisition of musical abilities and for the diagnosis and remediation of congenital amusia.

Experimental procedures

This research was approved by the ethics committees of the Montreal Neurological Institute, of the Institut Universitaire de Gériatrie de Montréal and of the University of Newcastle-upon-Tyne. Informed consent was obtained from all participants.

Scanning Protocol and Morphometric Analyses

T1-weighted MR sequences were obtained for all subjects on a 1.5 Tesla scanner at both sites according to the same MR acquisition parameters: 3D

fast field echo scan with 160 slices, 1 mm thick, TR = 22 ms, TE = 9.2 ms, flip angle = 30. The data from both samples were then processed in exactly the same way. Each T1-weighted image volume was corrected for signal intensity nonuniformity (Sled et al, 1998) and linearly transformed into standardized stereotaxic space (Collins et al, 1994). The transformed images were then classified into white matter (WM), grey matter (GM), and cerebrospinal fluid, using INSECT (Zijdenbos et al, 1996), an automatic tissue classification paradigm. The tissue-classified WM and GM maps were smoothed using a Gaussian smoothing kernel of 10 mm full-width at half-maximum, resulting in three-dimensional maps of WM and GM concentration. Following these processing steps, the data from the Montreal and Newcastle samples were then treated independently, so as to avoid cross-scanner artefacts (Ashburner and Friston, 2000). For each sample, regression analyses using the general linear model were performed to detect regions where WM / GM concentrations differed between amusics and controls, and to detect regions where WM / GM concentrations correlated with the behavioral scores on the six musical tests of the Montreal Battery of Evaluation of Amusia (Peretz et al, 2003). Thresholds for t -statistic-values were calculated according to random field theory (Worsley et al, 1996). Given the exploratory nature of the initial analysis in the Montreal sample, we employed a lenient statistical threshold of $P < 0.05$ (uncorrected for multiple comparisons) in order to maximize the possibility of capturing subtle tissue concentration differences. The significant peaks from the Montreal sample defined a volume of interest (VOI) that was then tested in the Newcastle sample. The Newcastle peaks that exceeded a t-threshold associated with this VOI were deemed significant at $P < 0.05$ (corrected for multiple comparisons).

References

Ashburner, J., and Friston, K.J. (2000). Voxel-based morphometry—the methods. Neuroimage 11, 805–821.

Ayotte, J., Peretz, I., and Hyde, K. (2002). Congenital amusia. A group study of adults afflicted with a music-specific disorder. Brain 125, 238-251

Boddaert, N., Chabane, N., Belin, P., Bourgeois, M., Royer, V., Barthelemy, C., Mouren-Simeoni, M.C., Philippe, A., Brunelle, F., Samson, Y., and Zilbovicius, M. (2004). Perception of complex sounds in autism: abnormal auditory cortical processing in children. Am J Psychiatry. 161, 2117-20.

Collins, D.L., Neelin, P., Peters, T.M. and Evans, A.C. (1994). Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. J. Comput. Assist. Tomogr. 18, 192–205.

Drayna, D., Manichaikul, A, de Lange, M., Snieder, H., and Spector, T. (2001). Genetic correlates of musical pitch recognition in humans. Science 291, 1969-72.

Duvernoy, H.M. (1991). The human brain: surface, three-dimensional sectional anatomy, and MRI (New York: Springer-Verlag).

Foxton, J.M., Dean, J.L., Gee, R., Peretz, I., and Griffiths, T.D. (2004). Characterization of deficits in pitch perception underlying 'tone deafness'. Brain 127, 801-10.

Hackett, T.A., Stepniewska, I., and Kaas, J.H. (1999). Prefrontal connections of the parabelt auditory cortex in macaque monkeys. Brain Res. 30, 45-58.

Hyde, K.L., and Peretz, I. (2004). Brains that are out of tune but in time. Psychological Science 15, 356-60.

Kalmus, H, and Fry, D.B. (1980). On tune deafness (dysmelodia): frequency, development, genetics and musical background. Ann Hum Genet. 43, 369-82.

Koelsch, S., Gunter, T.C., v Cramon, D.Y., Zysset, S., Lohmann, G.,

and Friederici, A.D. (2002). Bach speaks: a cortical "language-network" serves the processing of music. Neuroimage 17, 956-66.

Peretz, I., and Coltheart, M. (2003). Modularity of music processing. Nature Neuroscience 6, 688-691.

Peretz, I., Champod, S., and Hyde, K. (2003). Varieties of Musical Disorders : The Montreal Battery of Evaluation of Amusia. Ann N Y Acad Sci. 999, 58-75.

Tillmann, B., Janata, P., and Bharucha, J. (2003). Activation of the inferior frontal cortex in musical priming. Cogn. Brain Res. 16, 145–61

Trainor, L.J., and Trehub, S.E. (1994). Key membership and implied harmony in Western tonal music: developmental perspectives. Percept Psychophys. 56, 125-32.

Vinckenbosch, E., Robichon, F. and Eliez, S. (2005). Gray matter alteration in dyslexia: converging evidence from volumetric and voxel-by-voxel MRI analyses. Neuropsychologia 43, 324-31.

Watkins, K,E., Vargha-Khadem, F., Ashburner, J., Passingham, R.E., Connelly, A., Friston, K.J., Frackowiak, R.S., Mishkin, M., and Gadian, D.G. (2002). MRI analysis of an inherited speech and language disorder: structural brain abnormalities. Brain 125, 465-78.

Worsley, K.J., Marret, S., Neelin, P., Vandal, A.C., Friston, K.J. and Evans, A.C. (1996). A unified statistical approach for determining significant signals in images of cerebral activation. Hum. Brain Mapp. 4, 58–73.

Zatorre, R.J., Evans, A.C. and Meyer, E. (1994). Neural mechanisms underlying melodic perception and memory for pitch. J. Neurosci. 14, 1908–1919.

Zijdenbos, A.P., Forghani, R., and Evans, A.C. (1998). Automatic quantification of MS lesions in 3D MRI brain data sets: validation of INSECT. Proc. Int. Conf. Med. Im. Comput. Assis. Interven. (MICCAI), pp. 439–448.

Figure legends:

Figure 1: Behavioral results on the Montreal Battery of Evaluation of Amusia. Percentage of correct responses obtained by the congenital amusic participants relative to musically-intact controls in the melodic pitch tests (averaged over the key, pitch direction and pitch distance tests; abscissa) and the rhythm test (ordinate axis) of the Montreal Battery of Evaluation of Amusia.

Figure 2: VBM results of white matter concentration differences and voxel-based correlation with the melodic-key test. VBM results of white matter (WM) concentration differences shown for each sample (Montreal and Newcastle; left and middle columns) and their conjunction (right column). Each brain image corresponds to a thresholded map of t-statistic values superimposed on the average anatomical MRI of the corresponding sample. Images are shown as horizontal sections, and coordinates are in standardized stereotaxic space (Collins et al, 1994). In all images, the yellow arrows correspond to the pars orbitalis of the right inferior frontal gyrus (rIFG). In a) are the WM concentration differences for the group comparison between amusics and controls, b) shows the voxel-based correlations for WM concentration and the melodic key-violation test of the musical battery, c) shows the significant positive correlation of WM concentration as a function of increasing score (out of 30) on the key-violation test at the rIFG peak, and in d) is the overall conjunction across the two samples and analyses.

Figure 3: Conjunction results in three planes of section. Right inferior frontal gyrus (rIFG) peak of decreased white matter in the group comparison (amusics vs. controls) in the Montreal and Newcastle samples, and their conjunction in 3-planes of section: a) horizontal, b) saggital, and c) coronal slices. Each individual map was thresholded at $P < 0.05$ (uncorrected), and the conjunction results shown here were superimposed on the average

anatomical MRI of all subjects in both samples.

Supplementary Figure 1: VBM results of white matter concentration differences and voxel-based correlation with the memory test. VBM results of white matter (WM) concentration differences shown for each sample (Montreal and Newcastle; first and second columns) and their conjunction (third column). Each brain image corresponds to a thresholded map of t-statistic values superimposed on the average anatomical MRI of the corresponding sample. Images are shown as horizontal sections, and coordinates are in standardized stereotaxic space (Collins et al, 1994). In all images, the yellow arrows correspond to the pars orbitalis of the right inferior frontal gyrus (rIFG). In a) are the WM concentration differences for the group comparison between amusics and controls, b) shows the voxel-based correlations for WM concentration and the memory test of the musical battery, c) shows the significant positive correlation of WM concentration as a function of increasing score (out of 30) on the memory test at the rIFG peak, and in d) is the overall conjunction across the two samples and analyses.

Figure 1:

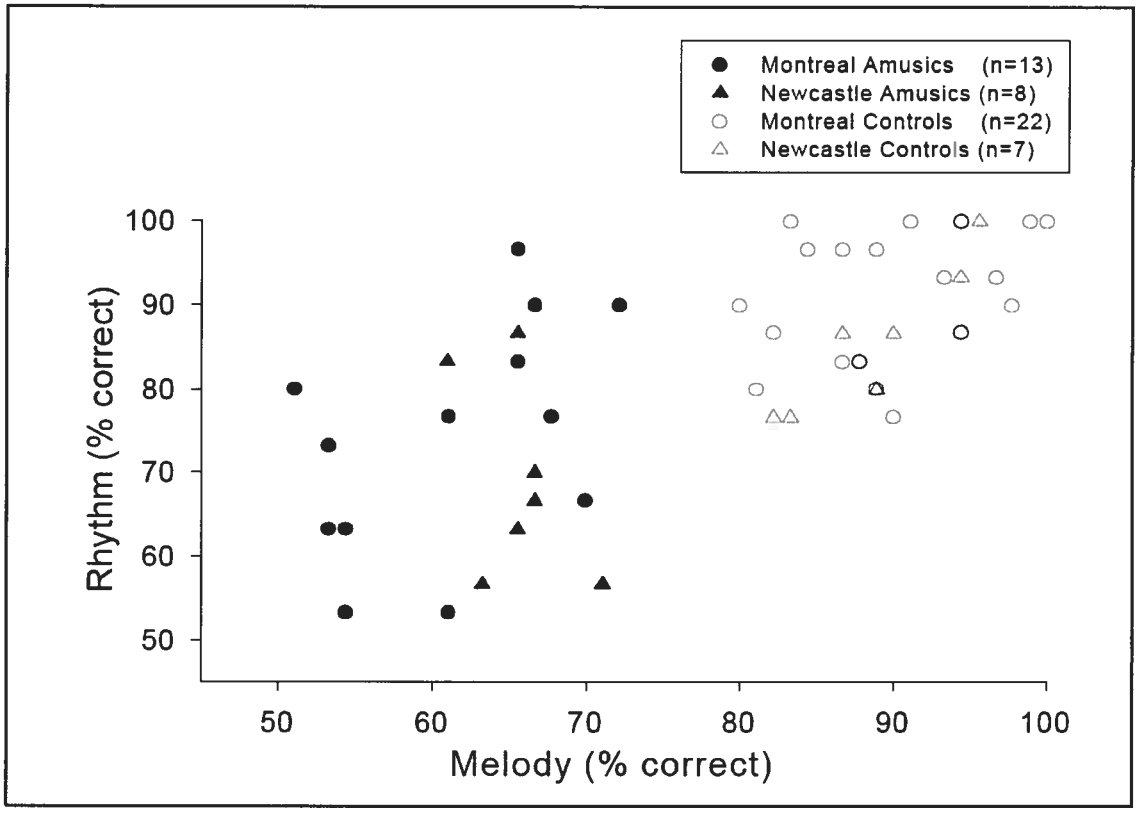

Montreal Amusics (n=13)
Newcastle Amusics (n=8)
Montreal Controls (n=22)
Newcastle Controls (n=7)
Rhythm (% correct)
100
90
80
70
60
50
50
60
70
80
90
100
Melody (% correct)

Figure 2:

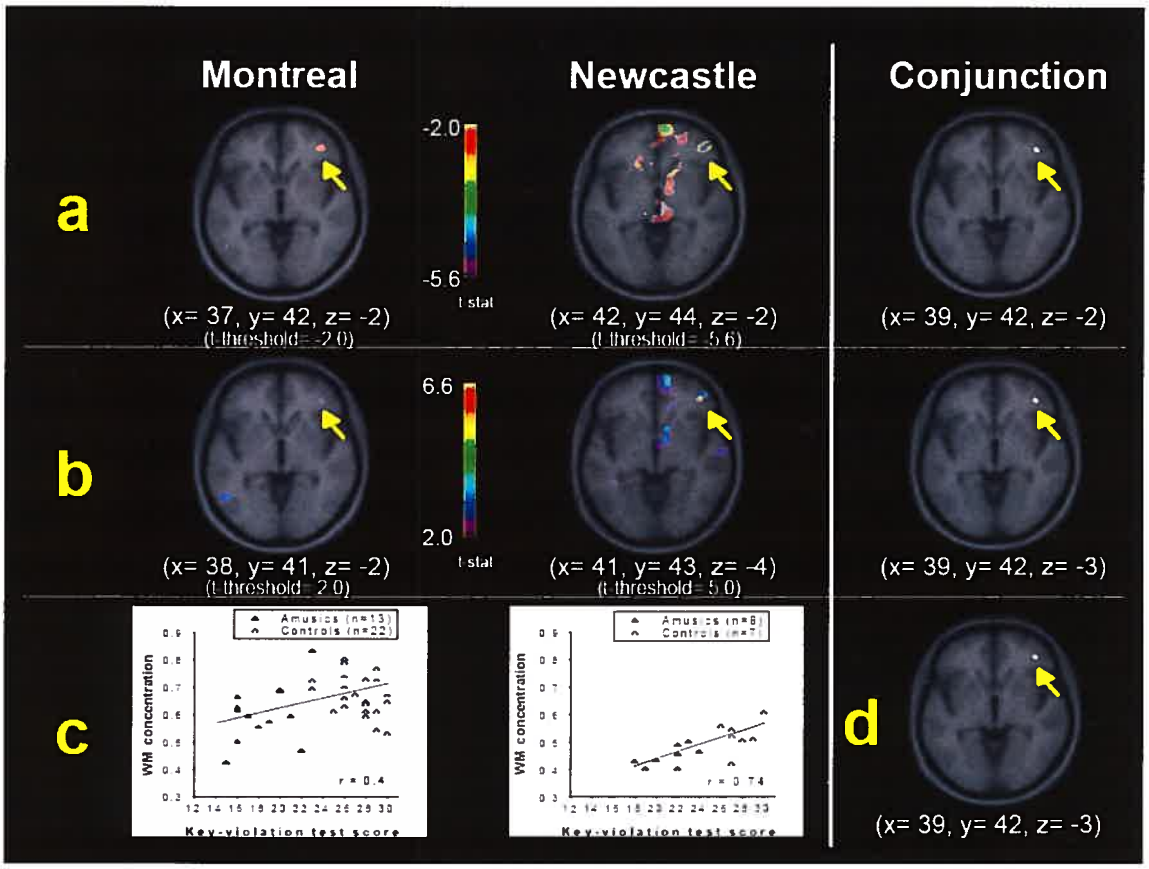
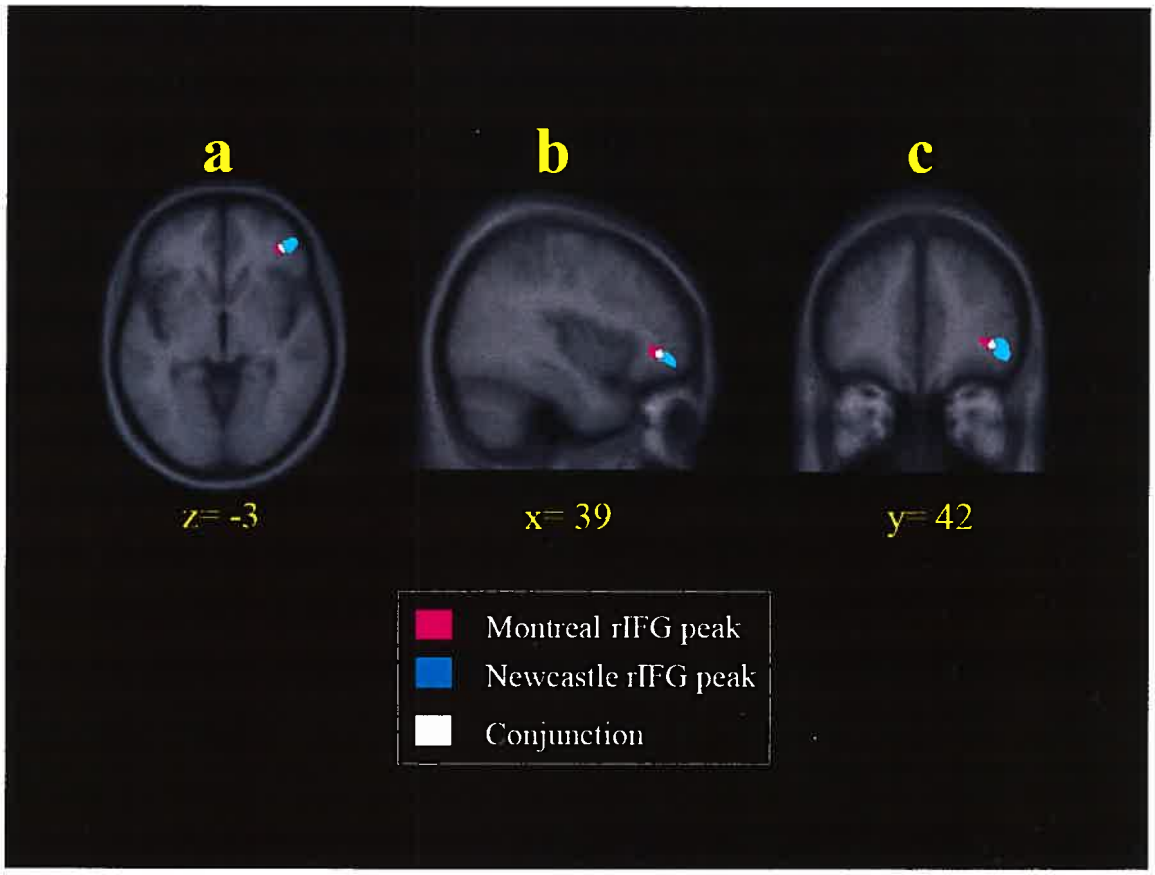
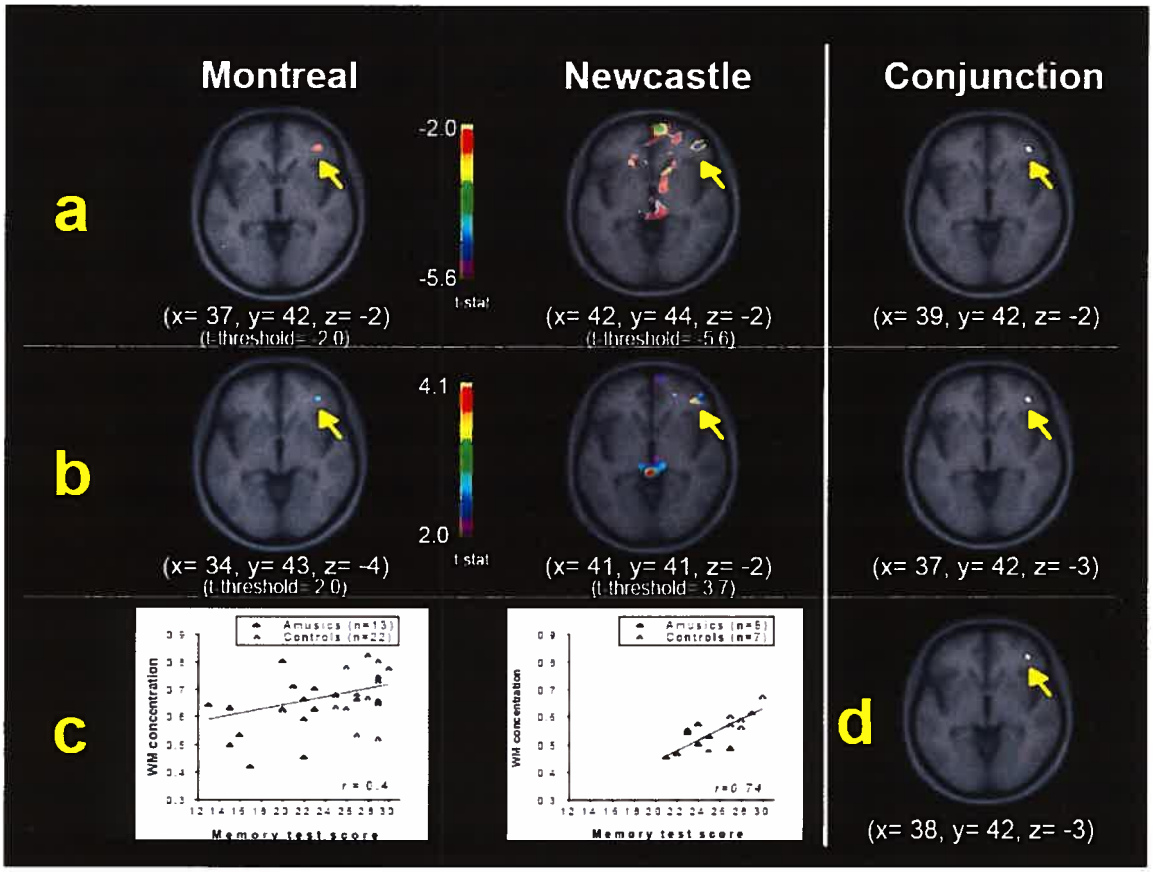

Montreal
Newcastle
Conjunction
a
-2.0
-5.6
t stat
(x= 37, y= 42, z= -2)
(t threshold = 2.0)
(x= 42, y= 44, z= -2)
(t threshold = 5.6)
(x= 39, y= 42, z= -2)
b
6.6
2.0
t stat
(x= 38, y= 41, z= -2)
(t threshold = 2.0)
(x= 41, y= 43, z= -4)
(t threshold = 5.0)
(x= 39, y= 42, z= -3)
c
WM concentration
Key-violation test score
r = 0.4
r = 0.74
d
(x= 39, y= 42, z= -3)

Figure 3:


a
b
c
z= -3
x= 39
y= 42
Montreal rIFG peak
Newcastle rIFG peak
Conjunction

Supplementary Figure 1:



GENERAL DISCUSSION

We have previously shown that congenital amusia is a genuine disability that exclusively affects music (Peretz, 2001; Ayotte et al., 2002). Afflicted individuals, who are otherwise unimpaired, have extreme difficulties appreciating, perceiving and memorizing music, despite their efforts to do so. In the present study, we conducted four studies to further investigate the behavioral and brain correlates of congenital amusia. The results from these studies offer several important scientific contributions. Overall, the findings inform us on abnormal and normal brain organization and shed light on the biological foundations of music. In particular, these findings serve to reveal which components are essential to music processing, which neural regions are important in acquiring normal musical competence, and to reveal the neural correlates of normal and abnormal pitch and time processing. The findings also serve to further document this disorder, and to motivate future studies on congenital amusia

Pitch, an essential component in music acquisition

The findings from the present thesis indicate that pitch is a key factor in normal musical development. For example, the findings from study 1 confirm our hypothesis that a likely perceptual cause of congenital amusia is a deficit in fine-grained pitch discrimination that would have prevented the normal development of the neural networks that ascribe musical function to pitch. Consistent with findings from a previous case study (Peretz et al., 2002), here we showed that a group of congenital amusic adults had problems to discriminate small changes in pitch. Based on the fact that amusics had problems to discriminate pitch changes including one semitone, and that this distance is critical to process melodies, we concluded that their pitch deficit may well account for their musical disorder. The pitch deficit was found to be specific to the pitch domain, since amusics had no problems to detect fine temporal changes. Thus, study 1 served to better document the nature of this acoustic pitch deficit over a group of amusic adults. Support for these findings comes from another group working on the same topic, that similarly

demonstrated a fine-grained pitch deficit in an independent sample of congenital amusic adults (Foxton et al., 2004).

This pitch deficit compromises the musical domain exclusively since amusics have no particular problem to distinguish pitch variations in speech (Ayotte et al., 2002). Speech intonation uses much larger pitch variations than music (Fitzsimons et al., 2001) and consequently, a problem in basic pitch discrimination may solely compromise the musical domain and not language. We suggest that the acoustic pitch deficit is not music-specific, but music-relevant (Peretz and Hyde, 2003). An important implication of these findings is that the brain would not be specialized for music, but rather, at an acoustic level, in the processing of fine spectral changes (Peretz and Hyde, 2003). This idea finds support in the theory of hemispheric asymmetry proposed by Zatorre and colleagues who argue that the right auditory cortex is specialized for fine spectral resolution as required in music, and the left for rapid temporal processing, as required in speech (Zatorre et al., 2002). Thus, one may consider congenital amusia as the mirror image of specific language impairments, where pitch is to music what time is to speech (Tallal et al., 1993).

The view that the brain may be specialized at an acoustic level, and not for music in particular, modifies the way in which congenital amusia, and the process of music acquisition in general, should be studied. If fine-grained pitch discrimination is critical to normal musical development, then early acoustic training should enhance certain aspects of musical processing such as the tonal encoding of pitch (Peretz and Hyde, 2003). Moreover, an impairment in fine-pitch resolution may entail problems in other domains, such as in the processing of tonal languages by native (amusic) speakers (Peretz and Hyde, 2003). Thus, findings from this thesis motivate future studies such as the effects of musical training on congenital amusic individuals, as well as investigations of tonal languages.

Structural integrity of right frontotemporal pathway is important for normal musical development

The study of congenital amusia serves to inform us on the neural correlates underlying normal musical competence. For example, in study 4 of the present thesis, we showed that one salient difference in the congenital amusic brain is an impoverished communication in a right-hemisphere based network involving the inferior frontal cortex and subserving the processing of pitch in musical contexts. The fact that this right frontal neural anomaly was related to a musical pitch-based task, fits nicely with functional evidence implicating this area in musical (tonal) pitch encoding, the ability to map pitches onto keys (Koelsch et al., 2002; Tillmann et al., 2003). This ability appears early in development (Trainor and Trehub, 1994), and is considered an essential process in music processing since it is instrumental in music memory (Hébert & Peretz, 1997) and serves to create expectations and feelings of surprise or satisfaction (Tillmann et al., 2000). The present results suggest that a defect in the tonal encoding of pitch may account for the highly selective nature of congenital amusia. Thus, the data indicate that the integrity of white-matter tracts in right frontal brain areas is key in acquiring normal musical development.

We do not conceive the decrease in white matter found in the right inferior frontal gyrus of amusic individuals as a cause of the disorder, but rather as a consequence of an anomalous wiring of the connections to the auditory cortex. We know from studies of the macaque brain that there are dual-processing streams in the auditory cortex (Hackett et al, 1999). There is an anterior (ventral) stream for the identification of auditory objects ("what"), projecting to ventrolateral prefrontal cortex (areas 10 and 12), and a posterior (dorsal) stream for the processing of auditory space ("where") projecting to dorso-lateral prefrontal cortex (areas 8a and 46). An analogous projection scheme has been proposed to hold for the human auditory cortex (Rauschecker and Tian, 2000). Thus, the finding in study 4 of this thesis of

reduced white matter concentration in a ventrolateral area of the right inferior frontal gyrus (area 12) of amusic individuals may be interpreted as a consequence of an impoverished communication along the ventral 'what' auditory stream.

From this view, it is possible that other neuranatomical differences in the amusic brain will be uncovered with further analyses, particularly in auditory cortical regions. To this aim, future morphometric analyses of the amusic brain are planned with diffusion tensor imaging (DTI). DTI is a magnetic resonance imaging method that can be used to measure local information about the structure of white matter within the human brain and thus provides a direct measure of brain connectivity (Le Bihan Dref et al., 2001). DTI has been used to effectively to reveal white matter structural abnormalities in developmental disorders such as autism (Barnea-Goraly et al. 2004) and dyslexia (Deutsch et al., 2005). Thus, it is a logical and promising technique to be used to examine white matter connectivity in the amusic brain. We are also currently undertaking cortical thickness measures in the amusic brain to provide a direct measure of grey matter differences (Lerch and Evans, 2004). As compared to voxel-based-morphometry, cortical thickness has the advantage of providing a direct quantitative index of cortical morphology. This technique is a choice method to be applied to congenital amusia since it has been recently used to demonstrate cortical thickness abnormalities in developmental disorders such as autism (Chung et al., 2005) and dyslexia (Casanova et al., 2004).

Innateness of musical pitch encoding

The structural anomaly found in the amusic brain fits with the idea that reduced connectivity with right frontal areas may be related to a genetic component that would contribute to problems in the musical encoding of pitch. Indeed, the melodic key-violation test in study 4 that was found to correlate so highly with white matter concentration in the right frontal area, is similar to a

task that has been shown to have a genetic element (Drayna et al, 2001). In a recent twin study, these authors tested 136 identical (monozygotic) twins and 148 fraternal (dizygotic) twins in their ability to detect out-of-key notes in popular melodies. Performance was more closely matched between identical (r=0.79) than between fraternal twins (r=0.46) (Drayna et al, 2001). These results were taken to indicate that the ability to map pitch onto musical keys may be genetically-linked. The recent discovery of a gene that is thought to underlie an inherited speech and language disorder (Lai et al., 2001; MacDermot et al., 2005), motivates the idea that there may similarly be a genetic component to certain aspects of music processing, for example, in the encoding of musical pitch. While we are far from discovering a 'musical gene', preliminary findings from our laboratory are consistent with the possibility that tonal pitch encoding may have a genetic component. All amusic individuals, and at least one of their first-degree relatives, have been shown to be severely impaired in a similar task to the one used in the Drayna et al. (2001) study, which required them to detect an out-of-key note in a conventional melody (Ayotte et al., 2002; Hyde & Peretz, 2005). In contrast, only one member out of all of the control families tested so far have a shown a similar impairment on this task (Peretz, in press). This study is currently ongoing in our laboratory. By documenting the distribution of this musical pitch disorder in the families of amusic individuals, we can obtain valuable information regarding its genetic origins.

Neural correlates of pitch and time processing

The role of right auditory cortex in fine pitch resolution in normal listeners

The findings from the present thesis inform us on the neural correlates of normal pitch processing. In particular, the findings from study 3 in which we used fMRI to investigate the neural basis of pitch pattern perception in musically-intact individuals, support the theory of relative hemispheric specialization of the auditory system (Zatorre et al., 2002). As expected,

brain activation was weighted to the right auditory cortex, which was more responsive with increasing pitch distance. Moreover, the results provide evidence that the right secondary auditory cortex has a finer pitch resolution than the left. While the right auditory cortex was sensitive to even fine pitch changes, the left was minimally sensitive to these, but was responsive to the large pitch changes. This study served as a basis for study 3, where we explored the neural correlates of pitch and time discrimination in congenital amusic individuals.

A deficit in processing temporally changing pitch patterns in congenital amusia

The findings from the present thesis also inform us on the neural correlates of abnormal pitch and time processing such as in congenital amusia. Prior to the research presented here, there was little known about the neural correlates of this musical disorder. In a previous ERP study (Peretz et al., 2005), amusics showed abnormal electrical brain responses relative to musically-intact controls in the right hemisphere when they had to detect a rare deviant tone in a sequence of repetitive standard tones. These results were considered to be a neural marker of the amusics' fine-grained pitch deficit. While the right auditory cortex of the amusics appeared to be intact, as indexed by a normal N1 component, the limited spatial resolution of the ERP technique may have precluded finding a subtle right auditory cortical anomaly. In study 3 of the present thesis, we improved on spatial resolution by using fMRI to investigate pitch and time discrimination in congenital amusia.

Contrary to expectation, amusics showed a similar pattern of brain activation as controls in processing pitch sequences, but did not show the same left-hemisphere asymmetry in processing the pitch patterns at various temporal rates. We suggested that these imaging data reflected that amusics may have problems to capture pitch changes when these are presented rapidly.

Results from a subsequent behavioral experiment confirmed this hypothesis. We suggested that amusics may not be able to apply normal specialized fine temporal analysis as a cascade effect of their deficits in both pitch distance and direction. The results from study 3 provide novel evidence that amusics have a more complex deficit than initially thought, involving pitch distance, pitch direction, and temporal resolution. These findings serve to motivate further studies to better understand the nature of the interaction of pitch and time processing in amusics. Preliminary data from our laboratory is consistent with the present findings that pitch discrimination in amusics deteriorates with increasing temporal rate to a greater degree than musically-intact controls (Pfeuty and Peretz, unpublished data).

Conclusion

In conclusion, the findings from this thesis have provided a better understanding of the behavioral and neural correlates of congenital amusia. We have shown that amusic individuals have a severe fine-grained pitch deficit that is thought to largely contribute to their musical problems. We have found a brain-behavioral correlate of a temporal pitch deficit in amusics that suggests that this pitch deficit may be more complex than first thought. Finally, we have found an important structural neural anomaly in the amusic brain in terms of a reduction in white matter concentration in the right inferior frontal gyrus of amusic individuals. This anomaly anomaly was related to pitch-based musical tasks, and is thought to account for the highly selective nature of congenital amusia. The data point to the integrity of white-matter tracts in right frontal brain areas as being key in acquiring normal musical competence. Thus, we have shown that congenital amusia is a rich area of study in that it informs us on abnormal and normal music development, and sheds light on the biological foundations of music. Further studies of congenital amusia should allow for a better understanding of the nature and causes of this music-specific disorder, and thus may someday offer remediation for afflicted individuals.

REFERENCES FOR THE GENERAL INTRODUCTION AND DISCUSSION

Ashburner J, Friston KJ. Voxel-based morphometry--the methods. Neuroimage 2000; 11: 805-21.

Ayotte J, Peretz I, Hyde K. Congenital amusia: a group study of adults afflicted with a music-specific disorder. Brain 2002; 125: 238-51.

Balzano G. The pitch set as a level of description for studying musical pitch perception. In Clynes M., editor. Music, Mind and Brain. Plenum Press; 1982.

Barnea-Goraly N, Kwon H, Menon V et al. White matter structure in autism: preliminary evidence from diffusion tensor imaging. Biol Psychiatry 2004; 55: 323-326.

Belin P, Zilbovicius M, Crozier S, Thivard L, Fontaine A, Masure MC, et al. Lateralization of speech and auditory temporal processing. J Cogn Neurosci 1998; 10: 536-40.

Boddaert N, Chabane N, Gervais H, Good CD, Bourgeois M, Plumet MH, et al. Superior temporal sulcus anatomical abnormalities in childhood autism: a voxel-based morphometry MRI study. Neuroimage 2004; 23: 364-9.

Burns EM. Intervals, scales, and tuning. Academic Press series in cognition and perception: A series of monographs and treatises 1999: 215-264.

Casanova MF, Araque J, Giedd J, Rumsey JM. Reduced brain size and gyrification in the brains of dyslexic patients. J Child Neurol 2004; 19: 275-281.

Chung MK, Robbins SM, Dalton KM et al. Cortical thickness analysis in autism with heat kernel smoothing. Neuroimage 2005; 25: 1256-1265.

Deutsch GK, Dougherty RF, Bammer R et al. Children's reading performance is correlated with white matter structure measured by diffusion tensor imaging. Cortex 2005; 41: 354-363.

Dowling W, Harwood D. Music Cognition. Academic Press; 1986.

Drake C. Psychological processes involved in the temporal

organization of complex auditory sequences: Universal and acquired processes. Music Perception 1998; 16: 11-26.

Drayna D, Manichaikul A, de Lange M, Snieder H, Spector T. Genetic correlates of musical pitch recognition in humans. Science 2001; 291: 1969-72.

Ehrle N, Samson S, Baulac M. Processing of rapid auditory information in epileptic patients with left temporal lobe damage. Neuropsychologia 2001; 39: 525-31.

Fitzsimons M, Sheahan N, Staunton H. Gender and the integration of acoustic dimensions of prosody: implications for clinical studies. Brain Lang 2001; 78: 94-108.

Foxton JM, Dean JL, Gee R, Peretz I, Griffiths TD. Characterization of deficits in pitch perception underlying 'tone deafness'. Brain 2004; 127: 801-10.

Fry D. An experimental study of tone deafness. Speech 1948; 1–7.

Geschwind N. The brain of a learning-disabled individual. Annals of dyslexia 1984; 34: 319–327.

Godefroy O, Leys D, Furby A, De Reuck J, Daems C, Rondepierre P, et al. Psychoacoustical deficits related to bilateral subcortical hemorrhages. A case with apperceptive auditory agnosia. Cortex 1995; 31: 149-59.

Grant-Allen. Note-deafness. Mind 1878; 10; 157–167.

Hackett TA, Stepniewska I, Kaas JH. Prefrontal connections of the parabelt auditory cortex in macaque monkeys. Brain Res 1999; 817: 45-58.

Halpern AR, Zatorre RJ. When that tune runs through your head: a PET investigation of auditory imagery for familiar melodies. Cereb Cortex 1999; 9: 697-704.

Hebert S, Peretz I. Recognition of music in long-term memory: are melodic and temporal patterns equal partners? Mem Cognit 1997; 25: 518-533.

Hyde KL, Peretz I. Brains that are out of tune but in time. Psychol Sci 2004; 15: 356-60.

Hyde KJ, Peretz I. Congenital amusia: Impaired musical pitch but intact musical time. In: Syka J, Merzenich M, eds. Plasticity and signal representation in the auditory system. New York: Springer Publishing Co., 2005; 291-296.

Jackendoff R. Consciousness and the Computational Mind. MIT Press; 1987.

Jeffries KJ, Fritz JB, Braun AR. Words in melody: an H(2)15O PET study of brain activation during singing and speaking. Neuroreport 2003; 14: 749-54.

Johnsrude IS, Penhune VB, Zatorre RJ. Functional specificity in the right human auditory cortex for perceiving pitch direction. Brain 2000; 123 (Pt 1): 155-63.

Kalmus H, Fry DB. On tune deafness (dysmelodia): frequency, development, genetics and musical background. Ann Hum Genet 1980; 43: 369-82.

Koelsch S, Gunter TC, v Cramon DY, Zysset S, Lohmann G, Friederici AD. Bach speaks: a cortical "language-network" serves the processing of music. Neuroimage 2002; 17: 956-66.

Lai CS, Fisher SE, Hurst JA et al. A forkhead-domain gene is mutated in a severe speech and language disorder. Nature 2001; 413: 519-523.

Large EW, Jones MR. The Dynamics of Attending: How People Track Time-Varying Events. Psychological Review 1999; 106: 119-159.

Le Bihan D, Mangin JF, Poupon C et al. Diffusion tensor imaging: concepts and applications. J Magn Reson Imaging 2001; 13: 534-546.

Lerch JP, Evans AC. Cortical thickness analysis examined through power analysis and a population simulation. Neuroimage 2005; 24: 163-173.

Liegeois-Chauvel C, de Graaf JB, Laguitton V, Chauvel P. Specialization of left auditory cortex for speech perception in man depends on temporal coding. Cereb Cortex 1999; 9: 484-96.

MacDermot KD, Bonora E, Sykes N et al. Identification of FOXP2 truncation as a novel cause of developmental speech and language deficits.

Am J Hum Genet 2005; 76: 1074-1080.

Mendez MF. Generalized auditory agnosia with spared music recognition in a left-hander. Analysis of a case with a right temporal stroke. Cortex 2001; 37: 139-50.

Merriam AP. The Anthropology of Music. Northwestern University Press; 1964.

Patterson RD, Uppenkamp S, Johnsrude IS, Griffiths TD. The processing of temporal pitch and melody information in auditory cortex. Neuron 2002; 36: 767-76.

Peretz, I. The nature of music from a biological perspective. Cognition, in press.

Peretz I. Processing of local and global musical information by unilateral brain-damaged patients. Brain 1990; 113 (Pt 4): 1185-205.

Peretz I. Auditory atonalia for melodies. Cognitive Neuropsychology 1993; 10: 21-56.

Peretz I. Can we lose memory for music? A case of music agnosia in a nonmusician. Journal of Cognitive Neuroscience 1996; 8: 481-496.

Peretz I. Brain specialization for music. New evidence from congenital amusia. Ann N Y Acad Sci 2001; 930: 153-65.

Peretz I, Ayotte J, Zatorre RJ, Mehler J, Ahad P, Penhune VB, et al. Congenital amusia: a disorder of fine-grained pitch discrimination. Neuron 2002; 33: 185-91.

Peretz I, Brattico E, Tervaniemi M. Abnormal electrical brain responses to pitch in congenital amusia. Ann Neurol 2005; 58: 478-82.

Peretz I, Champod AS, Hyde K. Varieties of musical disorders. The Montreal Battery of Evaluation of Amusia. Ann N Y Acad Sci 2003; 999: 58-75.

Peretz I, Coltheart M. Modularity of music processing. Nat Neurosci 2003; 6: 688-91.

Peretz I, Hyde KL.. What is specific to music processing? Insights from congenital amusia. Trends Cogn Sci 2003; 7: 362-367.

Peretz I, Zatorre RJ. Brain organization for music processing. Annu Rev Psychol 2005; 56: 89-114.

Phillips DP, Farmer ME. Acquired word deafness and the temporal grain of sound representation in the primary auditory cortex. Behav. Brain Res. 1990; 40 : 84–90.

Pinker S. How the Mind Works. Norton; 1997.

Perry DW, Zatorre RJ, Petrides M, Alivisatos B, Meyer E, Evans AC. Localization of cerebral activity during simple singing. Neuroreport 1999; 10: 3979-84.

Schönwiesner, M., Rubsamen, R. and von Cramon, D. Y. Hemispheric asymmetry for spectral and temporal processing in the human antero-lateral auditory belt cortex. Eur J Neurosci. 2005; 22: 1521-1528.

Schellenberg EG, Trehub SE. Natural musical intervals: Evidence from infant listeners. Psychological Science 1996; 7: 272-277.

Tallal P, Miller S, Fitch RH. Neurobiological basis of speech: a case for the preeminence of temporal processing. Ann N Y Acad Sci 1993; 682: 27-47.

Tervaniemi M, Medvedev SV, Alho K, Pakhomov SV, Roudas MS, Van Zuijen TL, et al. Lateralized automatic auditory processing of phonetic versus musical information: a PET study. Hum Brain Mapp 2000; 10: 74-9.

Tillmann B, Janata P, Bharucha JJ. Activation of the inferior frontal cortex in musical priming. Brain Res Cogn Brain Res 2003; 16: 145-61.

Tillmann B, Bharucha JJ, Bigand E. Implicit learning of tonality: a self-organizing approach. Psychol Rev. 2000;107:885-913

Trainor LJ, Trehub SE. Key membership and implied harmony in Western tonal music: developmental perspectives. Percept Psychophys 1994; 56: 125-32.

Tramo MJ, Bharucha JJ, Musiek FE. Music perception and cognition following bilateral lesions of auditory cortex. Journal of Cognitive Neuroscience 1990; 2: 195-212.

Trehub SE. Musical predispositions in infancy. Ann N Y Acad Sci 2001; 930: 1-16.

Trehub SE, Schellenberg EG, Kamenetsky SB. Infants' and adults' perception of scale structure. J Exp Psychol Hum Percept Perform 1999; 25: 965-75.

Turk I, Dirjec J, Kavur B (1996). The oldest musical instrument in Europe discovered in Slovenia? Archoloski vestnik. (English translation online at http://www.zrc-sazu.si/www/iza/piscal.html)

Vinckenbosch E, Robichon F, Eliez S. Gray matter alteration in dyslexia: converging evidence from volumetric and voxel-by-voxel MRI analyses. Neuropsychologia 2005; 43: 324-31.

Vos P, Troost J. Ascending and descending melodic intervals: statistical findings and their perceptual relevance. Music Percept. 1989; 6: 383–396.

Wallin, N., Merker,B., Brown,S. The origins of music. MIT press; 2000.

Warrier CM, Zatorre RJ. Right temporal cortex is critical for utilization of melodic contextual cues in a pitch constancy task. Brain 2004; 127: 1616-25.

Watkins KE, Vargha-Khadem F, Ashburner J, Passingham RE, Connelly A, Friston KJ, et al. MRI analysis of an inherited speech and language disorder: structural brain abnormalities. Brain 2002; 125: 465-78.

Yamasaki T, Goto Y, Taniwaki T, Kinukawa N, Kira J, Tobimatsu S. Left hemisphere specialization for rapid temporal processing: a study with auditory 40 Hz steady-state responses. Clin Neurophysiol 2005; 116: 393-400.

Zatorre RJ. Pitch perception of complex tones and human temporal-lobe function. J Acoust Soc Am 1988; 84: 566-72.

Zatorre RJ, Belin P, Penhune VB. Structure and function of auditory cortex: music and speech. Trends Cogn Sci 2002; 6: 37-46.

Zatorre RJ, Evans AC, Meyer E. Neural mechanisms underlying melodic perception and memory for pitch. J Neurosci 1994; 14: 1908-19.

Zatorre R, Peretz I. The Biological Foundations of Music. New York: The New York Academy of Sciences; 2001.